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Endocrinology

The Bulletin *of the*
Association *for the* Study *of*

Internal Secretions

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THE object of this Association is to correlate the work and interests of many physicians and students throughout the world who are engaged in the study of the internal secretions and organotherapy, and by concerted effort to broaden knowledge in this field.

This Association is not limited to specialists. It includes in its membership physiologists, pathologists and other investigators, in addition to a large number of physicians in active practice—leading men in this field in the United States and thirty other countries.

Every branch of medicine is represented. The orthopedist recognizes the importance of the internal secretions in relation to the physiology and pathology of bone development. The opthalmologist realizes the relation of the pituitary and the thyroid glands to his field; the pediatrician is especially interested because growth and development are controlled by hormones and many disorders of childhood are due to, or aggravated by, disturbances of the endocrine glands. Many disorders seen by the gynecologist are brought about by endocrine defects and there is a large and increasing literature dwelling upon the diagnostic and therapeutic phases of this subject. In internal medicine and surgery the endocrine glands figure constantly. Endocrinology, in short, is a matter of concern to the medical profession as a whole.

Reputable physicians and investigators are eligible for membership. The annual dues are $6.00, payable in advance. This includes a subscription to ENDOCRINOLOGY, the Association's by-monthly bulletin.

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ENDOCRINOLOGY is the official bulletin of the Association for the Study of the Internal Secretions. It is published in volumes of 600-800 pages. At present it appears as a bimonthly. It comprises original articles, authoritative reviews, critical abstracts of the endocrine literature and editorial discussions of timely topics.

Manuscripts of three types of original work are desired for publication:

a. *Clinical studies* of endocrine diseases and the part played by the endocrine organs as contributing factors in other diseases;

b. *Systematic studies* on endocrine therapy;

c. *Laboratory investigations* of endocrine problems.

Articles are accepted for publication with the understanding that they will appear in this journal only.

Manuscripts may be submitted in any modern language, and if found suitable for publication will be translated into English without expense to the authors. To insure a version, however, satisfactory to the author, it is desirable that the article be submitted, when feasible, in English.

Readers who encounter articles of endocrine interest in unusual periodicals or under captions not indicating such interest are requested to submit abstracts for publication.

Bibliographic form: Since ENDOCRINOLOGY is to a considerable extent a bibliographic journal, it is desirable that references should be given in *complete form,* quoting title of article, author, periodical, year, volume number and page. The references should be segregated on separate sheets for publication at the end of the article. Footnotes should be used sparingly and included with the text.

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Manuscripts may be addressed to the Editor, Prof. R. G. Hoskins, Harvard Medical School, Boston, Mass.., or to any of the members of the staff.

Correspondence relating to advertising and business matters should be addressed to Endocrinology, 1045-6-7 Rowan Bldg., Los Angeles, California.

TWELFTH ANNUAL MEETING OF THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

The Scientific Session of the Twelfth Annual Meeting of the Association for the Study of Internal Secretions was held at the Loring Theater, Minneapolis, Minn., Tuesday, June 12, 1928.

The morning session was called to order at nine o'clock and the following program was presented:

(1) "The Relationship of Iodine to Thyroid Hyperplasia and Function," by J. Earl Else, Portland, Oregon.

(2) "Iodine Deficiency Symptoms and Their Significance in Animal Nutrition and Pathology," by John M. Evvard, Ames, Iowa.

(3) "Exophthalmic Goiter and Adenomatous Goiter," by H. S. Plummer, Rochester, Minn.

(4) "The Relation of Infections to Goiter; Basal Metabolism Studies," by W. H. Cole, N. A. Womack and A. G. Heideman, St. Louis. Presented by Dr. Womack.

(5) "Congenital Goiter: Report of a Case Occurring After the Administration of Potassium Iodide to Mother During Pregnancy," by David P. Seecof and Clarence B. Ingraham, Denver. Presented by Dr. Seecof.

The above papers were discussed by Wm. Engelbach, St. Louis; Noble P. Barnes, Washington; R. G. Hoskins, Boston; Harvey Beck, Baltimore; Charles Elliott, Chicago; John M. Evvard, Ames, Iowa; John Y. Simpson, Louisville; J. Earl Else, Portland; H. S. Plummer, Rochester; N. A. Womack, St. Louis, and David P. Seecof, Denver.

(6) "The Relation of the Internal Secretions to Calcium Metabolism, Particularly the Thyroid and Parathyroid," by Joseph C. Aub, Boston.

Dr. Aub's paper was discussed by H. Lisser, San Francisco; H. S. Plummer, Rochester, Minn.; Wm. Engelbach, St. Louis, and Professor Green of Columbia, Mo.

The afternoon session was called to order at two o'clock and the following papers were presented:

(1) President's address, "The Uni-Glandular Origin of Pluri-Glandular Syndromes," by H. Lisser, San Francisco.

(2) "The Clinical Syndrome of Transitional Pituitary Adenomas," by Percival Bailey and Harvey Cushing, Boston. Presented by Dr. Bailey.

(3) "Hypophysectomized Puppies," by F. L. Reichert, San Francisco.

(4) "The Normal Proportions of the Different Constituents of the Human Hypophysis (A Statistical Study)," by A. T. Rasmussen, Minneapolis.

(5) "Recent Progress in the Investigation of the Posterior Lobe of the Pituitary Gland," by E. P. Bugbee and O. Kamm, Detroit. Presented by Dr. Bugbee.

The above papers were discussed by Wm. Engelbach, St. Louis; R. G. Hoskins, Boston; Emil Novak, Baltimore; Jos. C. Aub, Boston; H. Lisser, San Francisco; closing with Percival Bailey, Boston; A. T. Rasmussen, Minneapolis, and E. P. Bugbee, Detroit.

(6) "A New Source of Ovarian Follicular Hormone and Some Notes on Its Assay," by J. A. Morrell, J. R. Varley, and H. H. Powers, New Brunswick, N. J. Presented by Dr. Morrell.

H. LISSER, President.
F. M. POTTENGER, Secretary.

TWELFTH ANNUAL BUSINESS MEETING OF THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

The Twelfth Annual Business Meeting of the Association for the Study of Internal Secretions was held at the Loring Theater, Minneapolis, Minn., at five o'clock the afternoon of June 12, 1928.

The reading of the minutes was waived.

The report of the editor, Dr. R. G. Hoskins, was received. Dr. Hoskins mentioned several favorable features in connection with the publication of ENDOCRINOLOGY.

Moved by Dr. Engelbach that a vote of thanks be given the editor for his splendid work. Carried.

The Nominating Committee presented its report, recommending the following named persons for officers and members of the Council for the ensuing year:

President—Oscar Riddle, Cold Springs Harbor, N. Y.

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Joseph C. Aub, Boston

H. Lisser, San Francisco

Moved by Dr. Else that the by-laws be waived and that the secretary cast the unanimous ballot of the Association for the nominees. Carried.

The secretary then cast a ballot for the nominees and the president declared them elected.

A vote of thanks was given the retiring officers for services which they had rendered to the organization.

The report of the business manager, Mr. P. C. Mason, was then given and accepted.

On motion of Dr. Else a vote of thanks was extended to all the officers for their services. Carried.

Questions regarding the publication of the journal, membership, etc., were discussed by the organization, but no actions were taken.

On motion the meeting then adjourned.

H. LISSER, President.
F. M. POTTENGER, Secretary.

IMPORTANT NOTICE — CHANGE OF ADDRESS

The name of the building in which our Los Angeles office is located has been changed to the Rowan Building. Please note this change, effective June 1, 1928. A new building across the street will take the name "Title Insurance Bldg.," and this should not be used in future. The address now is 1045-6-7 Rowan Bldg., Los Angeles, Calif. This building is located at 458 South Spring St., corner Fifth Street.

NOTICE!

The Annual Assembly of the Inter-State Post Graduate Medical Association of North America will be held in the City of Atlanta, Ga., Oct. 15-19, inclusive, 1928. All medical men in good standing are privileged to register, and all the cordially invited to attend.

A complete program and folder of information will be mailed about four to six weeks in advance of the opening of the assembly, to all medical men in good standing, as listed in the latest Directory of the American Medical Association.

Edwin Henes, Jr., M. D., 445 Milwaukee St., Milwaukee, Wis., is Executive Secretary of this organization, and other information may be had by addressing him.

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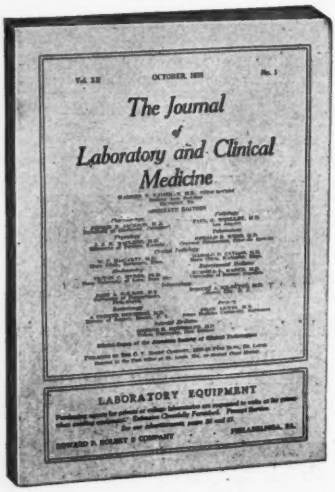

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Endocrinology

The Bulletin *of the*
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May-June, 1928

STUDIES OF THE ENDOCRINE GLANDS*

II. The Pituitary

ALLAN WINTER ROWE, PH.D.
AND
CHARLES HENRY LAWRENCE, M.D.
Evans Memorial
BOSTON

PART I

In a recent communication one of us (Rowe, 1) has presented the details of an objective method for the differential diagnosis of endocrine disorders, together with an analysis of a series of one thousand cases to which it has been applied. The present paper deals with the results obtained in the study, by this method, of a series of cases, four hundred in number, in which some form of pituitary malfunction was demonstrated as a primary etiological factor. As the full details of the method have been published in the earlier communication, it is enough here to state that a very thorough physical examination and the compilation of a detailed medical history are supplemented by a long series of laboratory tests, the significance of which

*Presented at the Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J., May 26, 1925.

has been demonstrated by elaborate preliminary studies. In addition, detailed examinations by the specialists of the consulting staff give supplementary information concerning indications of endocrine disease, and, even more significantly, the presence or absence of disorders of a non-endocrine etiology. The inadequacy of a single observation to establish a diagnosis except in the rarest instances has already been stressed in the preceding paper. Individual objective facts gain diagnostic significance only as they are interpreted in the light of a large number of correlated observations and measurements. Facts elicited are interpreted in terms of endocrine malfunction only after every known non-endocrine cause has been eliminated by observation and test. This does not preclude the recognition of coexisting endocrine and non-endocrine disorders, but does prevent grave omissions on the one hand, and seriously misleading diagnoses on the other. In a shortly forthcoming paper on non-endocrine disorders, cases illustrative of this point will be presented. In one, the entire picture, save only the blood morphology, was typical of thyroid dysfunction. The case was one of leukaemia.

In presenting this material no attempt can be made at a survey of the literature. The compendious monographs of Cushing (2), Blair Bell (3), Engèlbach and Tierney (4), Falta (5), Biedl (6) and others, together with the series of excellent articles in "Endocrinology and Metabolism" (7), give reviews which are as complete as the rapidly growing literature will permit. When to these earlier compilations are added the several hundred titles that yearly appear, the impossibility of adequate presentation is obvious. Reference will be made only to contributions, the details of which bear directly on the thesis in hand. Omission of recent papers implies no adverse opinion of their merit.

The present series of four hundred pituitary cases is selected from nearly two thousand patients referred for diagnosis. The presentation of so large a mass of data within reasonable compass offers manifest difficulties. The tabulation of averages offers the simplest solution, but here, in some measure, the means defeats the end. The algebraic summation of the results of opposing influences by its very nature destroys the magnitude and direction of deviations from the conventional normal which are of diagnostic significance. To illustrate: a judiciously

blended group of extreme thyrotoxicoses and myxedemas would exhibit a strictly normal average basal rate. Further, in any group of cases but a few will be of an advanced order, and the inclusion of many incipient cases betraying tendencies rather than an established condition will lessen the average magnitudes and hence the apparent significance of variation. On the other hand, with an adequate number of cases, because of these limiting conditions, variations of relatively small amount may assume a real significance.

An added complication arises, in the present instance, from the fact that the hypophysis consists of at least two, and possibly four, functional entities.

Waiving, in the interest of simplicity, the subtleties of dialectic, we shall designate as "hyperfunctional" those cases in which the observed facts equate with what is generally conceded to be the evidence of an over-activity. Equally, the "hypofunctional" group show a picture of relationships the opposite of the foregoing. The cases designated as "dysfunctional" are those in which the two lobes are demonstrably not at the same functional level, and includes those cases in which one or both lobes are undergoing functional involution.* This group contains a wide variety of conditions determined by the relative functional variations in two bodies, each with three potential levels of activity and seemingly well differentiated as to independent influence on metabolism. As might well be predicted, a very large percentage of the cases here reported fall in this category.

Yet another element of confusion arises from the fact that different disease pictures are engendered by the relation of the time of development of the glandular malfunction to the age, and particularly to the sex status of the individual. These differences have been well recognized and so frequently described as to require no further elaboration here. That the intermediate or end results of a given pituitary aberration will be greatly influenced in certain directions by the maturity of the individual, is established, and in any scheme for the presentation of data, sufficient differentiation must be employed to take cognizance of significant variations.

*The shifting sugar tolerance during the progress of acromegaly, so clearly demonstrated first by Cushing and his associates (8), is a case in point.

Recognizing the limitations implicit in this method of presentation of data, it remains only so to order the arrangement as to reduce these obscuring conditions to a minimum. While the group contains few of the spectacular cases of extreme malfunction which have been reported from other sources, all of the earlier cases, the study of which laid the foundation of the present generalization, exhibited clear-cut and unmistakable lesions demonstrated by previous surgical intervention, radiography or subsequent necropsy. Well established acromegaly prior to the onset of the involutional changes, is usually unmistakable. But the same definition is lacking in the other syndromes which bear the names of Froehlich, Lorain-Levi, and others.

From the clinical standpoint there is a certain possibility of confusion in the hypofunctional states of several of the endocrine group, and only by objective methods of great completeness of detail can they be differentiated with any measure of certainty.

Turning to the results of the study, the various physical measurements have been collected in the following table. The highest and lowest values observed for each measurement are included as giving an idea of the range of variation in each of the several quantities. In conformity with the convention discussed above, hypofunctional states are designated as "—," the complementary hyperactivities as "+," while the several types of dysfunction are grouped under the caption "±." The summary values are, in many instances, unduly influenced by the relative numerical preponderance of the dysfunctional group. The use of unweighted averages, however, would only introduce a different disturbing element.

In discussing these data it must constantly be borne in mind that the magnitudes recorded are possibly influenced by wholly extraneous factors of which no cognizance may be taken. Such an element as the percentage distribution of different races presenting widely different characteristics,* could well modify data obtained by two independent investigators. The

*In this connection, to ascribe racial peculiarities to varying levels of endocrine function, wholly ignoring the manifest influences of environment, nutrition, and climate, shows more enthusiasm than judgment. Further, these ethnic groups fail to show many of the bodily peculiarities that their alleged endocrine origin would presuppose.

seeming predominance of females over males in this series may be due to an inherent greater susceptibility on the part of the female, and equally could be referable to a greater frequency of recourse by that sex to medical aid. Our figures showing a greater incidence of the "hyper"-functional state in the male are not in accord with the far more comprehensive observations either of Sternberg (9) nor of Hinsdale (10). Our larger

TABLE I

PHYSICAL MEASUREMENTS

Observation		Unit	Gland Function			Grand Average
			−	±	+	
Number of Cases		400	**83**	**310**	**7**	
Sex	Male	%	**29**	**36**	**57**	**40**
	Female	%	**71**	**64**	**43**	**60**
Age	High	years	71	70	63	
	Low	years	9	6	17	
	Average	years	**32**	**33**	**42**	**33**
Height	High	cm.	195	189	172	
	Low	cm.	130	103	155	
	Average	cm.	**165**	**164**	**166**	**164**
Sitting Height	High	cm.	100	99	91.5	
	Low	cm.	69	56	85	
	Average	cm.	**87**	**87**	**88**	**87**
Sitting Height Index			**0.527**	**0.530**	**0.530**	**0.530**
Chest Girth	High	cm.	128	145	98	
	Low	cm.	58	54.5	67	
	Average	cm.	**86**	**81**	**84**	**82**
Weight	High	kgm.	150.0	180.0	78.8	
	Low	kgm.	21.6	15.7	54.9	
	Average	kgm.	**73.7**	**66.3**	**65.6**	**67.8**
Area	Average	sq.m.	**1.81**	**1.72**	**1.73**	**1.74**
Lung Volume	High	c.c.	6200	5400	3600	
	Low	c.c.	1330	600	2380	
	Average	c.c.	**3650**	**2900**	**3050**	**2930**

series of hypo- and dys-functional cases accord with the frequently recorded observation of a greater incidence in the female. Whatever the cause, the fact remains that in this group the females predominate in ratio of 3 to 2. The small number of the true hyperpituitary group makes certain of the absolute magnitudes of somewhat less significance than with the other two divisions. The differences in relative physical proportions of the two sexes comes in as an obscuring factor in the absolute figures here recorded. Both the relation of Sitting to Total

Height (Sitting Height Index) and of the former to the chest girth (not here reported), are definitely different in the two sexes. Presentation on a sex basis would, however, multiply data without adding much to the significance of the picture.

Clarity of outline can be secured by relative figures, using two sets of standards for the sexes, and this has been done in the later tables wherever it is found to be informative. The only really salient sequence here traceable is in the greater tendency toward obesity with the lower activities, and even here the heaviest subject was a boy weighing 180.0 kgm., with a pituitary dysfunction of the type most common in our experience in which the anterior lobe is under-, the posterior, overactive.

The apparently greater age of the hyperfunctional group accords well with the general observation of the more frequent occurrence of this condition in adult years, and the frequent prepubertal appearance of glandular failure.

As was stated above, absolute values are influenced by several extraneous factors, to allow for which would entail a complexity that would obscure the issue. Certain correlations have been suggested which allow for sex and occupational differences by the establishment of graded standards. One set of such correlations have been suggested by Dreyer (11). As one of us (12) has shown, only the Dreyer comparisons based on Sitting Height (designated "Trunk" by the author) are significant, the other correlations leading to exterpolations of a most misleading character. Further, it is a better practice to use but one occupational standard for each sex, varying the limits of tolerance to accord with individual habit. We have adopted Dreyer's male "A" and female "B" standards as most nearly conforming to observed American conditions. West (13) has also established correlations between lung volume (designated "Vital Capacity" by Dreyer), area, and standing height. Our practice has been to report the average of the Dreyer value with the average of the two West comparisons. By so doing a weight factor (through the area) is introduced without leading to the absurd values of Dreyer's weight comparison. For the reason given above, only West's male and female standards are used. With both the West and Dreyer comparisons it has been found that the female standards accord better with male children than

do those of the adults of their own sex. The results of these comparisons are given in Table II.

TABLE II

"VITAL CAPACITY" COMPARISONS

Observation		Unit	Gland Function			Grand Average
			−	±	+	
Weight	High	%	+123	+179	+28	
	Low	%	−23	−42	−11	
	+ Average	%	**+33**	**+27**	**+13**	
	%	%	73	62	71	65
	− Average	%	**−9**	**−13**	**−8**	
	%	%	29	38	29	35
	Net Average	%	**+22**	**+12**	**+7**	
Chest	High	%	+52	+65	+16	
	Low	%	−15	−24	−13	
	+ Average	%	**+14**	**+12**	**+7**	
	%	%	76	63	71	66
	− Average	%	**−7**	**−7**	**−7**	
	%	%	24	37	29	34
	Net Average	%	**+9**	**+5**	**+3**	
Lung Volume	High	%	+18	+20	−13	
	Low	%	−56	−62	−31	
	+ Average	%	**+8**	**+6**	−	
	%	%	19	10	0	11
	− Average	%	**−21**	**−22**	**−19**	
	%	%	81	90	100	89
	Net Average	%	**−16**	**−19**	**−19**	

The values given above possess a certain definite significance. The tendency of the pituitary case to over-weight is clearly shown, as well as the influence of the level of functional activity on this manifestation. The correlations between chest and weight are excellent. While the girdle type of obesity that suggests pituitary malfunction should influence the chest less than the hip measurement, increase in girth of the former may confidently be predicted.

The depression of observed over calculated lung volume is definite, and again might well be anticipated. Peabody (14) has shown the depressing influence of cardiac disease and of general weakness, and other writers have made similar observations (15). The significance here is in the relatively slight diminution (slightly less than one-fifth) of the predicted capacity. Further, the value is probably in excess of the truth, as the general obesity in this condition makes the West normal standards somewhat high. No correction is made for this, however, as the results thus obtained are better suited for the dem-

onstration of diagnostic differences in cases as actually met in practice.

The end results of certain phases of metabolism can best be evaluated by analysis of the urine, and certain of the observations permitting of tabular presentation are collected in Table III.

TABLE III

URINE MEASUREMENTS

Observation		Unit	Gland Function			Grand Average
			−	±	+	
Volume	High	c.c.	5800	3680	2000	
	Low	c.c.	330	350	860	
	Average	c.c.	**1360**	**1150**	**1280**	**1190**
Spec. Grav.	High		1.036	1.039	1.028	
	Low		1.005	1.007	1.012	
	Average		**1.018**	**1.019**	**1.019**	**1.019**
Albumin		%	**19**	**25**	**57**	**24**
Casts		%	**11**	**18**	**43**	**17**
Sugar		%	**0**	**25**	**71**	
"Urobilinogen"		%	**21**	**29**	**71**	**29**
Amylase Index	Average		**19**	**18**	**20**	**18**
Salol	Average	min.	**72**	**70**	**81**	**71**
Urea Curve	Normal	%	**54**	**50**	**0**	**49**
	Delayed	%	**14**	**11**	**33**	**12**
	Progressive	%	**5**	**7**	**0**	**6**
	Low	%	**27**	**32**	**67**	**33**
Phenol Sulphone Phthalein, 2-hour Elim.	Average	%	**52**	**51**	**55**	**51**

While the dissociation of diabetes insipidus from pituitary disease, suggested, among others, by Houssay (16), and more recently by Bourquin (17), as deriving from injury to the mammillary bodies, eliminates this condition in some measure from a priori inclusion in the hypophyseal group, it does not preclude the frequent observation of a pituitary polyuria. The contiguity of the controlling bodies to the endocrine gland implies frequent damage to them secondary to hyperplasia of the pituitary.

Elimination here is seen to be fairly normal in spite of an appreciable number of cases of lowered kidney permeability demonstrated by the other observations. The sequential relationship of the appearance of albumin and casts is well illustrated in the percentages of the three groups. Even more strik-

ingly does the incidence of glycosuria as an evidence of posterior lobe over-function manifest itself. This finding has been very frequently recorded, although many of the observers, even the more recent, persist in regarding the condition as a diabetes engendered by pituitary influence on the pancreas. The untenability of this position is soon to be discussed at length elsewhere.*

A striking and significant finding in this group of cases is the positive response of the urine to para-dimethylamino benzaldehyde, the "urobilinogen" test of Ehrlich. That this response depends upon the presence of urobilinogen, is hardly probable. Positive tests have been demonstrated by many in a variety of liver conditions, and one of us (1) has shown it in primary anaemia. Like so many color reactions in which an organic complex is the reagent, the test lacks in specificity and may well be given by a series of substances which need have only a single organic group in common. Its appearance in cases of pituitary disease is of a definite diagnostic import when the non-endocrine causes have been experimentally ruled out. The Salol test, of no great significance, approaches normality. Designed as a rough test of gastric motility, it is primarily dependent on kidney permeability. The provocative urea curves agree in substance with the urine analyses in implying a lowered level of kidney activity, and the Phthalein test offers such measure of confirmation as may be derived from any test subject to so many extraneous disturbing influences.

Summarized, it may be said that a disturbed kidney function seems to be concomitant to pituitary malfunction—probably by indirection through general metabolic disturbance,—that posterior lobe over-function frequently produces a glycosuria which is not diabetic, and that a positive response to para-dimethylamino benzaldehyde is shown by nearly one-third of the cases in this series.

It has been the practice of this laboratory to make nitrogen partition examinations on all urines analyzed. This serves the two-fold purpose of estimating the nutritional level of the patient,† and of indicating metabolic disturbance in abnormality

*Rowe, "Non-Diabetic Glycosurias." In preparation.

†For example, the obese patient who acknowledges a food intake of a glass or two of milk in the twenty-four hours, and whose 24-hour urine contains 25 grams of nitrogen. Equally valuable is the recognition of a partial protein starvation with its far reaching effects.

of the partition formula. As has been pointed out by one of us (18), it is not necessary to carry out an elaborate nitrogen metabolism experiment for these data to assume significance. The relative amounts of the several constituents in health depend, as was first shown by Folin (19), on the total nitrogen elimination, the endogenous and exogenous moieties of the several factors determining relative losses with lowered protein intake. The data from the nitrogen partitions are given in Table IV.

TABLE IV

NITROGEN PARTITION

Observation	Unit	Gland Function			Grand Average
		−	±	+	
Total Nitrogen.....Av....	gms.	9.37	9.28	10.56	9.33
Urea Nitrogen.....Av....	%	79.9	80.3	77.8	80.2
Uric Acid Nitrogen.....Av....	%	2.2	2.1	1.6	2.1
Ammonia Nitrogen.....Av....	%	4.3	3.7	4.8	3.8
Creatinin Nitrogen.....Av....	%	4.6	4.5	4.4	4.5
Residual Nitrogen.....Av....	%	9.0	9.4	11.4	9.4
% of Cases = or > 9%.....	%	39	54	71	51

The nitrogen averages show a general level of protein utilization well above Sherman's (20) maintenance level. It is true that they do not indicate a "luxury" consumption, but it should be borne in mind that the majority were hospital patients.

[For reasons that have never been fully explained, the average person during a hospital residence drops to a lower nutritional level for protein than his usual habit elsewhere. This is not due to any change in the dietary *per se;* it is our routine practice to give the patient not less than 1.5 grams of protein per kgm. body weight.* With the average weight as a basis, this would correspond to an elimination of some fifteen grams of nitrogen—making allowance for the fraction not absorbed. The actual output is but 60 per cent of the predicted. The phenomenon has been observed by every worker in this field, but so far as we know no attempt at an explanation of it has appeared.]

As the result of a long series of observations, partial report of which has already appeared (18), the residual or undetermined nitrogen partition has been assigned a value of 9 per cent

*Needless to say, in cases like that of our eleven-year-old boy weighing nearly four hundred pounds, this schedule fell far short of realization.

as the upper limit of normality. Folin (19) found values less than 8 per cent when the nitrogen output was reduced to less than four grams, but as the quantity is obtained by difference and incorporates all the analytical errors for the determined constituents, the higher value is felt to be more representative.

All of the groups show a level indicative of disturbed metabolism, and this is more marked in the hyper-active group, both in amount and in frequency of occurrence. If the hypo-active condition represented the terminal phase of a cyclic change—as is certainly partially the case in acromegaly—this might well be expected, the body re-establishing a new metabolic equilibrium at a lower level with the subsidence of the abnormal activities. This will not account for all cases but raises an interesting point for speculation in regard to a certain proportion of them. Another interesting feature is the relative and absolute increase in the uric acid elimination in the hypofunctional group. Falta and Nowaczynski (21) have noted an increase in uric acid output in acromegaly, but found a lowered elimination in a single case of head trauma which they diagnosed as "dystrophia adiposo-genitalis" from a tumor in the region of the hypophysis. In this latter instance the question may well be raised if this single patient may be regarded as typical of true pituitary disease. In the study on the residual nitrogen already cited, it has been shown that while the high values are due in part to increase in the amounts of substances normally present in very low concentration, there yet remain significant amounts of nitrogen which cannot be allocated to any known constituent. The nature of this residuum is now under investigation.

As the blood is the forerunner of the urine, the results of the routine examinations of fasting blood may next be considered.

In the main it will be seen that the blood chemistry bears out the implication of the urine findings as to the functional capacity of the kidney. The most striking feature is the high value for uric acid, and more particularly the large percentage of cases showing a high uric acid with normal levels for the other nitrogenous constituents. Some years ago Hammett and his associates (22) observed an increase in blood uric acid in four out of six experimental subjects to whom desiccated pitu-

itary extract was administered per os. The present results leave no doubt that a high blood uric acid, independent of the other nitrogenous elements of the blood and not deriving from nephritis or gout, is found in disease of the pituitary. The diagnostic significance of this fact is important.

TABLE V

BLOOD CHEMISTRY (AND SEROLOGY)

Observation	Unit	Gland Function			Grand Average
		−	±	+	
Non-Protein Nitrogen.....Av....	mgm.	32	33	36	33
% > 35 mgm.....	%	22	25	57	
Urea Nitrogen.....Av....	mgm	15	16	17	16
% > 17 mgm.....	%	12	16	29	
Uric Acid.....Av....	mgm.	3.6	3.8	3.8	3.8
Net* % = or > 4 mgm.....	%	24	33	20	31
Creatinin.....Av....	mgm.	1.5	1.5	1.6	1.5
Residual Nitrogen.....Av....	mgm.	15.2	15.1	17.1	15.1
Sugar.....Av....	mgm.	97	95	93	95
% > 120 mgm.....	%	1	1	0	1
% < 80 mgm.....	%	1	5	0	4
+Wassermann.....	%	0	0	0	0
+Kahn (presumptive).....	number	0	0	0	0
+Spinal Fluid.....	number	0	?	0	?
+Schwartz-McNeil.....	number	0	1	0	1

An interesting result is the normal blood sugar observed and, particularly, that the hyperfunctional group present the lowest average. In a single case which we have had under continuous observation for over four years, and which is to be described in detail elsewhere as well as noticed in this paper, we have recorded high blood sugar levels. These were the result, however, not of the pituitary tumor per se, but possibly to injury to the brain produced during treatment or the coexistence of a true diabetes. The details on this case (S-326, B-269, B-475) will be given briefly later in this paper. It will be noted that one case in the series is reported with a questionably positive spinal fluid examination. There was an earlier history of lues, seemingly properly treated, the single doubtful test together with a number of findings indicating a pituitary dysfunc-

*All demonstrated cases of nephritis and gout have been deleted.

tion. Incidentally, the case has cleared up on anterior lobe medication. Under the circumstances there seemed to be no impropriety in including this case in the series.

The data for the Blood Morphology are given in the next table.

TABLE VI

BLOOD MORPHOLOGY

Observation	Unit	Gland Function			Grand Average
		−	±	+	
Haemoglobin.....Av....	%	88	88	94	88
Erythrocytes.....Av....	10^6	4.94	5.01	5.36	5.00
Color Index.....Av....		0.89	0.88	0.88	0.88
Leucocytes.....Av....	10^3	7.9	7.8	8.5	7.8
P. M. N. Neutrophiles.....Av....	%	56	57	64	57
% = or > 75%.....	%	0	5	29	
Lymphocytes.....Av....	%	35	36	27	36
% = or > 33%.....	%	53	62	43	59
Eosinophiles.....Av....	%	2	3	1	3
Net % = or > 3%*.....	%	28	31	14	30
Monocytes.....Av....	%	7	4	8	4

The general picture is one of normality. The tendency toward a secondary anaemia reported by others (23), (24), (25), (5) has not been observed by us. In fact, the highest values are found in the frank hyperactive cases. Falta (5, p. 274) would seem to regard the reduction as characteristic of the later stages. Later (p. 312) in connection with hypophyseal dystrophy, he observes only a lowering of haemoglobin. Even this deviation does not appear in the present series. Isolated cases, naturally, exhibit some secondary anaemia. Our lowest haemoglobin was 50 per cent and the averages as given above are normal. A slight relative lymphocytosis finds expression in the average value, while nearly two-thirds of the individual subjects show lymphocytes above the conventional normal number. Falta (5, p. 312) makes the same observation on a small number of cases. Our observation has been that where the slightest increase in these cells is not observed, there is apt to be a marked decrease

* Cases in which a non-endocrine cause of eosinophilia was demonstrated have been deleted.

with values for the neutrophiles exceeding the normal. The lymphoid bloods, in our experience, are found with all the endocrine states—and in an appreciable number of non-endocrine conditions.

The other point of significance in the pituitary blood picture is the slight upward tendency of the eosinophiles. This fact has been reported by a number of observers (24), (5, p. 274, 312), (2), (26), and in single cases the observed percentage has assumed most significant proportions. Failure to eliminate non-pituitary causes, at least in the earlier cases, may account for some of these latter. Nearly one-third of the patients show this tendency even after all those demonstrating non-endocrine causes of eosinophilia have been deleted. The combination of an eosinophilia of moderate degree coupled with an increase in the uric acid of the blood, the other constituents exhibiting normal levels, is seemingly peculiar to pituitary disturbances. Such observations play an important part in establishing the general picture, all parts of which are necessary for definite diagnosis.

A most important chapter in the study of endocrine disorders deals with the respiratory metabolism. The data of our observations together with certain other informative concomitant measurements are collected in Table VII.

While the significance of the respiratory metabolism in endocrine disorders has been stressed by many writers, the striking variations produced by aberrant thyroid activity has tended to minimize consideration of the other ductless glands. This is seemingly particularly true as regards pituitary disease, and in the paucity of the published data is found one reason for the conflicting opinions which even today come to expression. Another and even more potent influence tending toward disharmony lies in the classification of pituitary conditions. While acromegaly is initially the result of a state of hyperfunction, the gland certainly may undergo functional involution, and in many cases in the later stages presents a laboratory picture which is the antithesis of that of the initial phase. As far back as 1912, Cushing (2, p. 22) emphasized this point and criticized adversely the findings of earlier investigators who had ignored this most significant observation. The designation of cases as

acromegalic without further qualification inevitably leads to confusion. Falta's analyses of the few cases of Magnus Levy (27), of Salomon (28), and of Bernstein and himself (5, p. 276) leads to the conclusion that uncomplicated acromegaly does not increase the basal metabolism, confirming the opinion of his quoted authorities. Confusion of the glycosuria of this condition with diabetes, and the assumption that the latter greatly increases metabolism, is one factor leading to his erroneous conclusions.

TABLE VII

RESPIRATORY METABOLISM

Observation	Unit	Gland Function			Grand Average
		−	±	+	
Basal Metabolism Deviation					
High	%	−4	+33	+23	+33
Low	%	−24	−28*	+14	−24§
+ Average	%	−	+8	+18	
%	%	0	8	100	
− Average	%	−15	−13	−	
%	%	100	92	0	
% > + 10%	%	0	2	100	
% between +10% and −9%	%	19	34	0	
% = or < −10%	%	81	64	0	
Blood Pressure					
Systolic Av.	mm.	117	113	165	
% < 110 mm	%	27	39	0	
Diastolic Av.	mm.	72	73	95	
% < 65 mm	%	26	23	14	
Pulse Rate Av.	per min.	72	72	83	72
% = or < 70 per min	%	43	43	14	
Respiration Rate Av.	per min.	14	15	14	15
% = or < 10 per min	%	11	9	0	
Temperature Av.	deg. F.	98.4	98.0	98.3	98.1
Alveolar CO_2 Av.	mm.	40	39	38	
% > 35 mm	%	57	67	71	66
% = or < 30 mm	%	5	3	0	3

The slight rise in basal rate observed by Benedict and Joslin (29) in diabetics without emaciation and confirmed by the latter's more extended observations (Joslin, 30), is usually more than compensated by the low nutritional level incident to the condition. This was originally pointed out by Lusk (31), and since confirmed by numerous other observations (32). Benedict and Homan's (33) hypophysectomized dog showed a definite decrease. Snell, Ford, and Rowntree's (34) observa-

*Complicated by partial inanition.
§Uncomplicated. See Note 1.

tions are scarcely pertinent, as of their seven cases five were of diabetes insipidus, a condition not certainly directly referable to pituitary disorder. Means (35) found a lowered rate in obesity of pituitary origin, an opinion more recently confirmed by others. Boothby and Sandiford (36) analyze thirty cases of acromegaly showing respectively 50 per cent over +10 per cent, 43.4 per cent with the conventional normal range of +10 to —10, and 6.6 per cent below the latter figure. These values equate perfectly with the varying functional level of glandular activity incident to the disease. Less easy to explain are the same authors' report on fifty-eight cases of "hypopituitarism" in which with 53.5 per cent below —10 per cent and 34.5 per cent in the normal range, they report 6.8 per cent (4 cases) with rates above +16 per cent. The warrant for including these latter under the diagnostic caption, is questionable. In the light of the experience of this laboratory they would seem far more probably dysfunctional types in which the anterior lobe still manifested some measure of over-activity. We have had opportunity to study several patients (a typical case protocol is included in the later discussion) over an extended period during which, as the result of their own decision, they remained without treatment. In these, the slow involution of glandular activity has been directly apprehensible, and the terminal phase, a true hypopituitary state with lowered basal rate and greatly increased sugar tolerance. Boothby (37) concludes, however, that "there is very little evidence that the secretion of any part of the pituitary gland . . . acts as a calorigenic agent." A number of other papers might be cited, but they would serve only to add to the contradictory opinions contained in the representative articles discussed above. Analysis of all existing data, irrespective of opinion, would seem to show that an over-activity of the anterior lobe conditions a moderate rise in the basal rate, and that the complementary failure produces an equivalent depression. There is an interesting suggestion of correlation in the facts that the anterior lobe is that portion of the gland essential to life, and that the great majority of cases of pituitary disease presenting well marked symptoms, show a lowered activity of this portion. Even in acromegaly, when the hyper-active phase obtains long enough to produce the striking structural changes characteristic of the syndrome, there is a defi-

nite tendency toward a recession of activity to an ultimate hypofunctional end state.

Before turning to the data of the present report it may not be inappropriate to re-emphasize one point. The diagnoses here presented are not the result of a single measurement apparently confirming a series of subjective evidences suggestive of some classic syndrome. They are, on the contrary, based upon a long series of carefully executed tests, the significance of each of which has been thoroughly defined by preliminary studies both with normal controls and cases whose surgical history defined the underlying pathology. These concrete facts were taken as the basis for the interpretation of the equally carefully acquired results of the physical examination and the subjective elements of the medical history. Finally, no one bit of evidence was accepted as indicating endocrine malfunction until every non-endocrine potential cause of such fact had been ruled out by test and observation. Finally the patients have been submitted to the therapeutic test of the indicated medication with observed improvement in clinical condition and laboratory findings. It may seem that undue emphasis is laid on this aspect of the work, but the record of diagnostic contradictions which were a genetic factor of this whole study makes us feel that this consideration is of basic and fundamental importance.

In the table given above it will be observed that the extremes of variation in the uncomplicated cases fall between —24 per cent and +33 per cent. The prevailing downward tendency is shown by the dominant fraction exhibiting values below —10 per cent. In the earlier stage of over-activity there is an unmistakable increase in the basal rate which, as the figures in the present series show, has never exceeded a moderate amount. In the small group of purely hyper-active cases, all adults, there were evidences of acromegaly in every patient. The downward tendency of the blood pressure, as was noted by Cushing in his series, is clearly manifest. Individual cases may fall below a systolic reading of 100, but the tendency is toward a moderate decrease falling short of the levels seen with the other endocrine glands. The seeming hypertension of the over-active cases is probably not due to the well known pressor action. Several of the cases in this group had a complicating cardio-renal

condition and, while a specific influence is not definitely ruled out, conservatism would reject it. The fall in blood pressure recorded in the course of acromegaly does not necessarily presuppose an initial hypertension. The average pulse rates are normal—in the hyper-functional group, a little raised—but in the two large groups nearly one-half were below 70. Inspection of a series of cases shows a definite tendency downward, but rarely does the rate assume the low level of the thyroid failure. The respiration rate is seemingly not affected by this nor, in fact, by any of the endocrine glands except the thyroid. A rapid rate can usually be referred to some exciting cause other than the gland function. Body temperature shows normal averages with but moderate departures in the individual cases. Alveolar carbon dioxide shows equally normal tensions. Two-thirds of these cases are above the conventional low normal limit, and only three present a level suggestive of an existing acidosis. To summarize then, the level of functional activity of the anterior lobe produces like deviations of moderate degree in the basal rate. The blood pressure and pulse manifest a downward tendency—exception has already been noted in the pure hyper-functional states—while the remaining observations conform substantially to the generally accepted normal values.

As the respiratory exchange is seemingly controlled by the anterior lobe, so the carbohydrate metabolism is generally regarded as reflecting the functional level of the posterior lobe of the gland. The data for this observation are found in Table VIII.

Before discussing the table, a few points may be explained. First, galactose is the sugar used, for reasons discussed in full elsewhere (38a, b, c, d, e), and the tolerance is determined by the appearance of sugar in the urine, it having been shown by one of us (38b) that the relationship of the dose to this level determines the shape of the so-called 'diagnostic curve. Further, while the male gonad has no influence on the galactose tolerance, with the female the opposite is the case. Normal tolerance ranges from the twenty grams of the prepubertal girl, through the forty of the adult woman to a post-menopausal level between thirty and forty. Pregnancy produces a lowering, first to thirty and ultimately to the prepubertal level of twenty, returning gradually to the original normal level after delivery. For this

reason, the expression of the tolerance dose in grams is misleading, and percentage variations from the individual's normal must be substituted. For the sake of uniformity, a like convention is adopted with the data of the male group.

TABLE VIII

GALACTOSE TOLERANCE

Observation	Unit	Gland Function			Grand Average
		−	±	+	
Male					
Dose.....High.....	gms.	70	60	20	
Low.....	gms.	40	5	5	
% above Normal.....	%	100	5	0	
Average Deviation of Dose.....	%	+73	+67	−	+70*
% equal Normal.....	%	0	13	0	
% below Normal.....	%	0	82	100	
Average Deviation of Dose.....	%	−	−50	−53	−52*
Female					
Dose.....High.....	gms.	120	80	20	
Low.....	gms.	30	5	10	
% above Normal.....	%	100	5	0	
Average Deviation of Dose.....	%	+74	+80	−	+77*
% equal Normal.....	%	0	2	0	
% below Normal.....	%	0	93	100	
Average Deviation of Dose.....	%	−	−53	−67	−60*
Summary					
% above Normal.....	%	100	5	0	
% equal Normal.....	%	0	6	0	
% below Normal.....	%	0	89	100	
Average + Deviation*.....	%	+74	+74	−	+74*
Average − Deviation*.....	%	−	−52	−60	−56*

A cursory inspection of the table demonstrates that the pituitary exercises a profound influence on the capacity of the organism to utilize carbohydrate. Examination of the dysfunctional group demonstrates further that the posterior lobe exhibits a tendency toward over-activity as marked as is that of the anterior toward under-activity. The numerical predominance of this group is certainly not fortuitous, as these cases are drawn from a group of nearly two thousand patients submitted for diagnostic study. That the superior limits should exceed the inferior, is to be expected from the numerical relationships. In fact, it is somewhat surprising that they show so

* Not weighted for relative number of cases.

close an agreement. The magnitudes speak for themselves and require no discussion. Obviously, the tolerance for galactose offers a valuable diagnostic point.

With the general differential picture of the three types of malfunction portrayed with certain inherent limitations in the preceding tables, the consideration of certain other pertinent matters not susceptible to tabular analysis may next claim attention.

Part II

In spite of the important advances that have been made in our knowledge of the pituitary gland during the past ten years, there is still much ignorance in regard to it, and especially in regard to the effect of disturbances in its function as contrasted with the results of tumor growth involving the organ upon bodily nutrition and metabolism. Due largely to the work of Cushing (39) and his collaborators much more is known concerning "surgical" pituitary disorders than those not demanding operative intervention.

This lack in regard to functional disturbances is due largely to the fact that, acromegaly excepted, there has been no certain method of establishing the diagnosis of disturbed pituitary function in any individual patient save by surgery or autopsy, and a painstaking analysis of cases in which the diagnosis was in many instances uncertain has not appealed to those to whom abundant material was available.

This paper comprises an analysis of clinical and laboratory findings in a series of patients in whom the diagnosis of pituitary malfunction seems reasonably established by clinical symptoms, laboratory findings, and the progress of the condition while under observation. The laboratory data are based on an analysis of 400 cases; the clinical findings embrace only one hundred.

There are several reasons for choosing this smaller number of cases for clinical analysis. First, all the patients in this smaller series have come under the immediate observation of one of us (C. H. L.) so that there has been a fair chance properly

to evaluate the symptoms and signs presented; second, the number seems sufficiently large to permit reliable conclusions; and third, it is the same as the number of acromegalics and patients with pituitary tumors recently reported by Davidoff (40) and Frazier and Grant (41), respectively.

In contradistinction to their patients all of those comprising the clinical section of this paper had hypofunctional disturbances of the pituitary, that is, either hypofunction of both lobes, or that condition described by Cushing (39), in which the anterior lobe is underactive while the posterior lobe is either normal or overactive. Inasmuch as it is impossible to distinguish between these conditions clinically, they are all grouped together in this analysis.

CLINICAL FINDINGS

In tabulating our clinical findings an attempt has been made to follow the plan used by Davidoff (40) in order that a comparison of findings might be easily made. Such a comparison brings to light very important points of difference and similarity between the two groups.

Incidence

Functional disturbance of the pituitary other than that caused by tumor of the gland is considered by the majority of physicians to be a rare condition, and important more as an interesting curiosity than as the cause of important disturbances of body function. This was our own point of view at the beginning of this study, but as our method of diagnosis has become more reliable, we have found that the pituitary is no more immune to disturbances of function than is the thyroid or the pancreas—its humbler position in medical thought is due not to its relatively infrequent involvement, but to the fact that this often exists unrecognized. In a series of 1000 cases examined in our clinic, 65 per cent have been found to have definite and significant disturbances of metabolism of endocrine origin. Of these, 12 per cent have presented symptoms and laboratory findings diagnostic of thyroid hypofunction; 14 per cent of ovarian dysfunction; 1.3 per cent of Addison's disease; while 28.4 per cent have been classed as disturbed pituitary function.

On the basis of these figures we are forced to the conclusion that disturbance of pituitary function is more common than is generally appreciated, but that the cause of symptoms produced by early or moderate disturbances is not generally recognized. Unless the patient exhibits definite acromegaly, giantism, or marked obesity of the pituitary type, the possible connection of hypophyseal function with the syndrome is usually not even considered. Yet Davidoff states that "the surgically verified cases also show that hypophyseal adenomas *without* acromegaly are about five times as frequent as those *with* acromegaly." If adenomata of the pituitary gland produce their most characteristic symptom only once in six times, it is not illogical to believe that disturbances in its function may often be present without giving rise to so-called pathognomonic symptoms, which allow a tentative and tenuous diagnosis to be made by inspection. Our conclusion concerning the incidence of disturbed pituitary function in so far is supported by proven facts.

Race. All the patients in this service were members of the white race, as were Davidoff's. Beyond this our analysis does not go, as the birthplace of the patients was not recorded, and in these days of wholesale immigration it is impossible to determine the nationality of a patient by the character of his patronymic. Our impression is that the majority were born in America, and that of those whose names were diagnostic the largest number of patients of foreign extraction were Jewish. This may be due to the population from which the majority of our patients come, or to a real susceptibility of the Jewish race to endocrine instability.

Sex. In our series there were 68 females and 32 males. At first sight this does not seem to agree with the findings of other observers (42) (43) who find acromegaly, at least, equally distributed between the two sexes. In Eidelsberg's (44) series of cases of hypopituitarism, however, the distribution was 55 per cent females and 45 per cent males. Reference to our larger series shows a predominance of males in the hyperfunctional, a preponderance of females in ratio of 2 to 1 in the dysfunctional and nearly 3 to 1 in the hypofunctional groups. The preponderance of females in our series is doubtless due in some part to the fact that men find it more difficult to take time for

hospitalization, so long as their illness is not incapacitating. Another factor may exist in the type of the disorder.

Age. The age of the patients at the time they entered the clinic is given in the following table:

TABLE IX

Age in years	Number of patients
1-10	2%
10-20	30%
20-30	22%
30-40	17%
40-50	20%
50-60	8%
60-70	1%

The extremely low figure for the first decade is undoubtedly unreliable. Metabolic studies on young children require special apparatus and special cooperation on the part of the patient. Undoubtedly the figure would be higher were we able to study satisfactorily all the children under ten years of age who present themselves at the hospital. It is significant, however, that between ten and twenty years are noted the greatest number of patients. Undoubtedly this is due to the fact that puberty occurs in this decade. In talking with these patients one is impressed with the large number who connect the beginning of their complaint with puberty, and the undoubted increase in endocrine activity during that epoch is an important factor in activating a potential functional weakness of the pituitary. The importance of its integrity for normal sexual development is well known, and our figures serve only to accentuate the fact that puberty is an important factor in changing a potential pituitary failure into an overt form. The sudden drop in incidence in the sixth decade also suggests the intimate association of the pituitary and sex functions.

An attempt to determine accurately the age of onset of symptoms in our series was unsuccessful, because of their gradual nature and the tendency of patients to connect their complaints with some manifestly unimportant event. Puberty, or its absence long after it should have occurred, was the most common single datum obtained.

The next largest group, all women, dated the beginning of their complaints from the birth of their first baby, irrespective

of their own age, while a somewhat smaller number presented themselves because of sterility. It is manifestly impossible to determine the duration of complete sterility unless one concludes that it existed from birth, or earlier. The significant fact is the large number of patients in whom pituitary malfunction is connected in some way with demands for increased activity due to some phase of the sexual life.

Occupation. No important relationship between occupation and pituitary disturbance could be detected.

FAMILY HISTORY

In only one case was there a definite history of acromegaly in a near relative. In ten cases there were one or more instances of abnormal height in near relatives. In eight cases there was a story of family obesity similar in distribution to the patient's. Nine patients gave apparently reliable stories of diabetes in near relatives. In three per cent, thyroid disorders appeared in the history of the immediate family, and in seven per cent there was the statement that some near relative had had "gland trouble." The significance of this last statement is open to question, but exclusive of that number, and of those with a family history of obesity, there is a history of definite endocrine disorder in some near relative in twenty-three per cent of our patients. As in diabetes (45) and thyroid disorder [see Janney (7)] there is evidence that the integrity of pituitary function is subject to inheritable factors.

MARITAL HISTORY

Only fifty-five per cent of our patients were married. This figure is much lower than Davidoff's. If, however, we exclude those below twenty years from our calculation, the figure will be raised to eighty per cent, which is not significantly different from his. We are inclined to agree with him that this small number of marriages is due in considerable degree, to the blighting effect of pituitary malfunction on gonadal activity and sex life.

Of the productive marriages, the resulting number of children was one in 28 per cent, two in 23 per cent, three in 31 per cent, and four, five, and six in 6 per cent each. In this

group of patients who were not sterile the pituitary disturbance, so far as could be determined, did not antedate the pregnancies.

To summarize, only 55 per cent of our patients were married, 36 per cent of those married were sterile, and an additional 28 per cent had less than the normal average number of children, convincing evidence of the importance of disturbances of pituitary function in influencing fertility. Were we certain of the potency of the patient's mate in each marriage and of the relation of beginning of symptoms to the date of marriage in every case, the figures would be still more significant. A study of sterility is now being carried on in our clinic which we hope will contribute important information on this question.

PAST HISTORY

Development. Eighty patients gave histories of normal physical and mental development. This coincides nearly with Davidoff's figure for acromegalics (40). In 13 per cent there was a history of significant early obesity or abnormal skeletal growth. Seven per cent had had difficulty in keeping up with children of their age in school. None of these figures is particularly significant, and the criteria are unsatisfactory. No conclusions can fairly be drawn from them. Much more significant are the findings in regard to puberty. Of 92 patients beyond normal puberal age, delayed or absent sexual development was present in 32, almost 35 per cent. Of these, two were males, thirty were females, although of the entire group thirty were males and sixty-two females. In other words, nearly 50 per cent of the female patients and only 6 per cent of the male patients beyond the normal puberal age showed delayed sexual development. It is, of course, far easier to determine accurately the onset of maturity in the female than in the male, and it is probable that the apparent low percentage of delayed sexual development in males is to some degree explained by the lack of a definite symptom. It would hardly account, however, for the entire difference in the figures. Here is a question which demands further investigation.

The answer may lie in the greater susceptibility of females to endocrine disturbances in general, and it is possible that this susceptibility is due to the fluctuating endocrine balance asso-

ciated with menstruation and pregnancy. The apparent demonstration by Frank (46) of the appearance and disappearance of a female sex hormone in the circulating blood is of possible significance in this connection.

Previous Illnesses

The incidence of previous illnesses in our series of patients is shown in the following table:

TABLE X

PAST HISTORY

Operations	57%	40%—removal of tonsils and adenoids 8%—appendectomy. 9%—miscellaneous.
Trauma	7%	2%—involving head. 5%—other parts.
Scarlet Fever	19%	
Typhoid	7%	
Pneumonia	7%	
Influenza	19%	
Tonsilitis	58%	
Meningitis	5%	
Mumps	37%	
Miscellaneous	12%	3%—rheumatic fever 3%—sinusitis. 3%—tuberculosis. 3%—malaria.
Relation to Present Illness		Definite 1%—pregnancy. Possible 4%—infections. Not established—95%.

Two significant facts appear in this table: one, that the onset of the condition is so gradual that only 5 per cent of patients can connect it in any way with preceding illness; the other, that there is an extremely large percentage of definite focal infection in these patients. Even discounting the present enthusiasm for removing tonsils, the fact that 40 per cent of our patients had had tonsillectomy cannot be easily dismissed. Appendectomy is an operation concerning which there is little hesitation at present, yet the table shows only one appendectomy for each five tonsillectomies. The incidence of tonsils so diseased as to demand removal must, therefore, be accepted as significant.

In this connection, the figures for tonsillitis are confirmatory and significant. Only patients who had had frequent and repeated attacks of "sore throat" are included in the 58 per cent charged with tonsillitis, yet the incidence is significantly greater than that of mumps, a common disease of childhood, easy of identification. The conclusion may fairly be drawn therefore that tonsillar infection and disturbed pituitary function coexist in a significantly large number of cases.

The question as to which condition causes the other is as yet not definitely answered, but observation of our patients after removal of diseased tonsils strongly suggests that focal infection is in many associated with the depression of the glandular activity. The following case is significant.

PROTOCOL 1

The patient was a tall, thin school girl, 17 years of age, presenting amenorrhea as her chief complaint. The menses had never been established and she had always been below her predicted weight. During the past year she had grown very rapidly.

The family history is without significance, except for a paternal aunt who did not menstruate until after her sixteenth birthday.

The patient's past history records only a few minor ailments in childhood and a mild attack of influenza in 1920. But for her present difficulties, the general level of her health has been excellent.

Physical Examination: The patient was a tall, very thin, moderately nervous girl, intelligent and co-operative; with a height of 67 inches in her shoes and a weight of 92½ pounds in her underwear. The skin and mucous membranes were somewhat pallid. The teeth showed evidence of much dentistry. The tonsils were large and scarred and the pillars injected. She had infantile breasts; there was neither pubic nor axillary hair, and examination by the rectum showed an almost infantile uterus. The pulse was slightly high and the blood pressure definitely low.

Laboratory Examination: The urine was practically normal, except for a very slight trace of albumin. The blood showed 75 per cent haemoglobin, normal erythrocyte count, a slight leukopenia and a substantially normal leucocytic formula. The smear showed a moderate achromia. Blood chemistry showed a low non-protein and urea nitrogen and high uric acid. a blood sugar value of 120, a value probably above the truth. The basal rate was reported as identical with prediction. This value was undoubtedly high.

Comment: The delayed menarche, absence of breast development, and body hair, the small uterus and the patient's body configuration are typical of hypophyseal infantilism. Pelvic examination under anæthetic confirmed the findings by rectum, and eliminated other pelvic disorder.

Treatment and Progress: The patient was given pituitary extract, anterior lobe, beginning with 8 grains daily and rapidly increasing to 16 grains. Tonsillectomy was advised but refused.

On January 15, 1925, her weight was 108¼ pounds; hemoglobin, 90 per cent; blood pressure, 100-70. The breasts had developed a

little and there was a slight growth of axillary and pubic hair. A week ago she had severe cramps in the pelvis, lasting 8 hours, the breasts being sensitive at that time.

On June 10, 1925, her weight was 113½ pounds. She had not menstruated, but the breasts were now normal in size and the pubic and axillary hair normal in amount.

On December 3, 1925, her weight was 115 pounds. Her general health was excellent, with no menstruation or molimina.

June 24, 1926. Four days ago menstruation began and persists. She was feeling well. Her weight had increased to 119½ pounds. Her height was 69½ inches. The basal metabolic rate was —4 and the pulse rate 72.

July 15, 1926. The gynaecologist reports that the uterus is much larger, being practically normal in size.

January, 1927. The patient reports having had one short period, and one attack of pelvic cramps lasting 12 hours.

Tonsillectomy was performed in March, 1927.

June, 1927. The patient reports another menstrual period, of normal character. She complains of frequent frontal and vertical headaches, beginning about four weeks ago. At the same time, there is occasional mild vertigo. She is advised to diminish the dose of pituitary extract to 10 grains daily.

December, 1927. Menstruation has continued regularly since June. The headache disappeared when medication was diminished. she reports herself in perfect health.

Comment: The interesting features in this case are: First, the response to oral pituitary medication; and, second, the effect of removing focal infection. The idea that pituitary extract is not effective when given by mouth is, we believe, unjustified. Undoubtedly, the dosage usually employed is insufficient, and in certain patients even large doses produce no typical results. Focal infection is a probable factor in many cases showing negative results. Conditions within the digestive tract possibly interfere with absorption in others. The possibility of success is, however, great enough to justify treatment by oral medication, provided one is prepared to push the dosage if necessary, and to remove any inhibiting factors which exist in the individual patient. The whole question of endocrine medication will be considered at length in a series of papers now in preparation.

The permanent establishment of menstruation following removal of the tonsils, together with the simultaneous appearance of headache relieved by diminishing the dose of pituitary extract can only be interpreted as indicating an improvement in pituitary function when the focal infection was eliminated. It is our belief that focal infection, especially of the tonsils, is a definite etiological factor in pituitary hypofunction. No other significant relationship appears in the table.

THE EXISTING CONDITION

One can hardly use the term "disease" in relation to departures from health due to disturbed function without definite organic change. The majority of our patients were able to "carry on" in spite of their handicaps, but their lack of health

was sufficient seriously to interfere with their efficiency and enjoyment. The symptoms and signs as recorded in the clinical histories, are tabulated below.

TABLE XI

Symptoms and signs as recorded in clinical histories:

Symptom	*Incidence*
Enlargement of acral parts	6%*
Enlargement of sella turcica on x-ray examination	5%
Disturbance of menstruation	51%†
Headache	34%
Complete amenorrhoea	8%‡
Visual disturbances	7%
Excessive perspiration	3%
Hypertrichosis	28%
Drowsiness and lethargy	8%
Changes in weight (greater than ±10%)	73%
Diminished libido	11%
Asthenia	36%
Low blood pressure (less than 120 mm. Hg.)	28%
Paraesthesias	20%
Polyphagia	4%
Polydipsia	1%
Constipation	29%
Vomiting (with present illness)	10%
Rhinorrhoea	1%
Photophobia	1%
Uncinate attacks	3%
Failing memory	1%
Decrease of body hair	0%
Persistent lactation	1%
Failure of breasts to develop	1%
Epistaxis	0%
Choked discs	3%
Vertigo	14%
Tinnitus	17%
Deafness	15%

*Definite acromegaly.
†Of females over 14 years of age.
‡Of females over 14 years of age.

A comparison of the above findings with Davidoff's table of symptoms (40) shows certain interesting similarities and differences. Those symptoms which are in all probability due to disturbed nutrition show a strikingly similar incidence in both tables; those due to enlargement of the sella, present in large numbers in his table, are rare in ours.

Enlargement of acral parts appears, at first sight, to be an exception to this rule. Davidoff, however, studied only patients having such enlargement, while our study comprises all types of disturbed pituitary function. Moreover, we have excluded from our table many patients in whom disturbances of acral growth, or asymmetry of development was definitely present although there was not the facial distortion characteristic of acromegaly. If we were to include in our table all those patients who showed asymmetrical skeletal growth, the figure would be greatly increased. From the diagnostic point of view, bodily asymmetry is one of the most important stigmata of disturbed pituitary function, past or present.

Distortion of the sella demonstrable by x-ray was absent in all but 5 per cent of our patients. This is, of course, no evidence concerning the function of the pituitary. Disturbance of its function may exist without affecting the sella outline and an abnormal sella shadow does not prove that the pituitary is in any way involved. This fact has been emphasized by Camp (47) and is well illustrated by the following case.

PROTOCOL 2

The patient was an English woman, 44 years of age, who was referred because of severe headaches. During the past twenty years these have occurred at fortnightly intervals. The pain starts suddenly, is severe and throbbing, and usually begins in the frontal or temporal region, later extending to the vertex. The pain lasts from one to three days and ends spontaneously and abruptly. During its course nothing affords relief. There are no associated disturbances, neither nausea, vertigo nor visual aberration. Eight years ago drainage of one maxillary antrum was performed in the hope of affording some relief. Following this, there was freedom from pain for about six months. At that time the patient had an attack of influenza, subsequent to which the headaches returned and have persisted to the present, gradually increasing in frequency and severity.

Family History. The father died of pneumonia at the age of 36; the mother of arteriosclerosis at 64. Four sisters and one brother are living; one sister has died of cancer. All members of the family are abnormally tall.

Past History. The patient reports several minor ailments and scarlet fever in childhood. She was undersized until 16 years of age, and then grew rapidly for the next two years, attaining her present height of 5 feet 7 inches. She had rheumatic fever at 18, and influenza as above noted. The catamenia was established at 16 and has apparently been perfectly normal.

Physical Examination shows a tall, somewhat emaciated white woman with prominent lower jow. Beyond infected tonsils the findings were normal.

Laboratory Examination. The general urine picture was normal, except for one specimen showing a trace of albumin. The blood showed a slight relative lymphocytosis, but was otherwise not significant. The blood analysis gave low normal values for all the nitrogenous constitutents, with a normal blood sugar. The basal metabolic rate was —4 per cent. The patient was 20 per cent under weight. The blood pressure shows a mild degree of hypertension. The sugar tolerance is normal, as are the eye findings. Radiography of the skull showed a large deep sella (Plate 1), and a slight thickening of the membranes lining the maxillary sinuses. On the basis of the appearance of the sella a diagnosis of slow growing pituitary tumor had previously been offered.

Comment. Although the x-ray findings suggested a pituitary tumor, the patient's general condition and more definitely the normal laboratory examination and eye findings failed to support such a diagnosis. The x-ray also disclosed infected sinuses, and these were operated upon successfully, but a mastoiditis developed as a sequel. Since her recovery from this latter condition she has had no more severe headaches, the condition being confined to a rare mild attack of brief duration.

Note. If a diagnosis of pituitary tumor on the radiographic findings of the sella is ever justifiable, the picture presented in this patient would seem to be an ample warrant. The laboratory examination, however, was wholly negative, and, more significantly, the result of treatment would seem to indicate a purely non-endocrine cause of the patient's difficulty. We do not feel that a single observation of this type ever forms a firm basis for a diagnosis, and that the carefully compiled history and physical examination, supplemented by complete metabolic studies cannot be supplanted by any single observation.

In a study of pituitary function, radiography of the sella turcica is valuable because it helps to establish the presence or absence of tumor, not because it affords any information concerning functional disturbance.

Of much greater importance, we believe, is the evidence gained by a complete study of the eye grounds and visual fields. This was done, in our patients, by Dr. W. D. Rowland, to whom our thanks are due for his most important contribution to this study. His findings in 84 cases are tabulated in Table XII

The importance of studies of the eye in pituitary disturbance has been emphasized in a recent article by Frazier and Grant (41). We have found it of enormous value both in estab-

lishing the diagnosis of pituitary disturbance, and in separating the cases in which tumor is present from those in which there is no growth. Even in the latter group contraction of the visual

TABLE XII

EYE FINDINGS IN EIGHTY-FOUR CASES

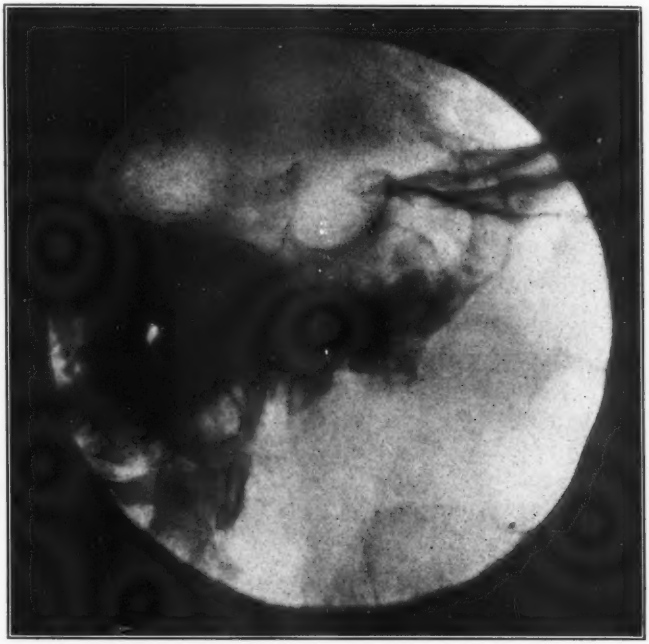
Choked Discs	3%
Yellow Discs	19%
Hazy Discs	10%
Optic Atrophy	1%
Vessels Sclerosed	3%
Contracted Visual Fields	29%
Enlarged Blind Spots	64%

fields is not uncommon, and definite enlargement of the blind spots is the rule rather than the exception. The character of the contraction of the visual fields frequently leaves little doubt that they are due to the pituitary condition, especially as sinus disease has been ruled out in our patients. Whether the blind spot enlargement is due to pressure from a pituitary which is slightly enlarged or to nutritional changes is not so certain, but from the point of view of diagnosis this finding is extremely important. The lack of subjective visual disturbances is no evidence that the visual fields are normal for we have seen a considerable number of patients with markedly contracted fields who stated that there was no difficulty with the vision. That such contractions may be caused by simple hyperplasia or functional disturbance of the pituitary is evident from the work of Finlay (48), Erdheim and Stumme (49) and Carvill (50).

Disturbances of the Menstrual Cycle. Fifty-nine per cent of our female patients showed disturbance of menstruation, if we consider those adults in whom menstruation was entirely absent with those in whom it was present but abnormal. In four of our patients with amenorrhoea, menstruation had never appeared, and examination showed juvenile pelvic organs. In four others, menstruation had been established for varying periods and the pelvic organs were not demonstrably abnormal.

The disturbance of the menstrual cycle in our series was characterized by late menarch, short duration of catamenia and scantiness of flow, increased intermenstrual interval, and ab-

PLATE 1



Case B-412. X-ray of sella showing probable tumor. Patient gave no evidence of functional pituitary disease.

sence of significant pain. These changes in menstrual behavior are, we believe, characteristic of an associated pituitary hypofunction as contrasted with other endocrine disturbances. Menstruation may be markedly disturbed by abnormal thyroid function, but in that condition menorrhagia and shortened intervals are as common as the reverse, while in ovarian hypofunction pain is commonly a prominent symptom. The group of disturbances mentioned above, especially if found in a patient with asymmetrical physical development demand a careful study of the functional level of the pituitary.

Weight Disturbances. In this series 73 per cent (65 per cent in the larger series) of the patients showed a variation from normal weight, as calculated by the West and Dreyer Standards, of more than 10 per cent. This difference is not necessarily pathological, but forms a fair basis for classification. Of those whose weight was not normal, 57 per cent were overweight. Underweight was found chiefly in adolescents showing the Levi-Lorain type of disturbance, and seldom amounted to more than —20 per cent, the maximum deficiency recorded being —30 per cent. Overweight while by no means limited to adults, was more common among those over twenty, and was of more marked degree. As a rule overweights of 40 per cent were not uncommon, and the maximum in this group was 60 per cent. The obesity showed almost without exception a predilection for the middle third of the body, the neck, wrists, and ankles remaining nearly normal. Characteristically, these patients gain weight very rapidly, and under certain conditions lose it rapidly, only to regain it again. The obesity is stubbornly resistant to dietary treatment, it being usually impossible to reduce weight and keep the patient well at the same time. It seems logical to suppose that the obesity is connected with the disturbed carbohydrate metabolism of these patients, and from a practical point of view, rigid curtailment of carbohydrate intake is more effective than general reduction of calories in combating this type of obesity.

Besides the definite tendency to abnormal weight, our patients showed clearly the effect of pituitary activity on skeletal growth by the number above "normal height." Of those who had passed the growth period, 25 per cent of the males were

over 6 feet, and 18 per cent of the females were over 5½ feet in height. The definite upper limit of normal height is difficult to fix, and these figures are given merely to make clear the definite tendency to increased height in these patients. Not only was their height above the average, but in the majority there was a history of very rapid growth during a limited period of time, most often coincident with or shortly after puberty. Such rapid growth, as well as the abnormal height, must mean a glandular hyperactivity at the time of their occurrence, and we believe that in many of our patients this hyperactivity preceded the state of hypofunction which existed when they were studied. Certainly neither symptom furnishes any valuable evidence concerning the state of pituitary function when the patient comes for examination—they merely suggest that at some time there has been a hyperactivity of the gland. This may still be present, or function may have returned to normal, or have swung still further into the hypoactive phase.

The Skin. The most frequent cutaneous abnormality encountered in our series was hypertrichosis, which was definitely present in 28 per cent, mostly women. Abnormal loss of hair was not present in any of our patients, if we except absence of body hair in the cases of delayed puberty. The changes in the hair consist in altered quality and distribution. The hair of the head, axillae and pubis is thick, oily, and vigorous, and there is a marked tendency toward increased hairiness of the trunk and limbs, most striking in women, in whom hair is usually not found in those sites.

Other than the hypertrichosis, 23 per cent of our patients are described as having some cutaneous abnormality such as roughness, dryness, or excessive oiliness. Cold skin, so common in hypothyroidism, was not noted. Neither were definite eczemas, which are also common in hypothyroidism. Vasomotor instability, frequently encountered in patients with depressed ovarian function, was conspicuous by its absence.

The teeth which might be expected to participate in disturbance of nutrition affecting the hair and skin, were described in definitely abnormal in 28 per cent of our patients. The variations from normal were rapid and general decalcification, malposition, or delayed eruption. The two latter conditions were

always associated with other signs of delayed development, while decalcification was present in the obese patients with increased tolerance for sugar. The exact relation of carbohydrate and calcium metabolism is not known, but our findings bear out the idea held by many dentists, that the teeth of individuals who consume large amounts of sugar are usually soft.

The Thyroid Gland. Twenty-three per cent of our patients showed symmetrical, elastic enlargement of the thyroid gland. All of them had basal metabolic rates below normal. For a complete discussion of thyroid enlargement in pituitary disease the reader is referred to the recent paper of Cushing and Davidoff (51). As yet the interrelation of the two conditions is not understood, and a discussion of theories must be omitted here. The important fact from our point of view is that thyroid enlargement and low basal metabolic rate do not always mean hypothroidism, and do not, therefore, always demand treatment with thyroid extract.

The Tonsils. Attention has already been directed to the seemingly important role played by tonsillar disease in pituitary malfunction, as judged from the clinical histories. The physical findings in our series lend confirmation to the idea already expressed, for in only 25 per cent of the patients were normal tonsils present. Forty per cent had had their tonsils removed, and in an additional thirty-three per cent the tonsils, in the examiner's opinion, were definitely infected. The criteria for this judgment were the presence of injection of the tonsillar pillars, with large or irregular tonsils from which pus could be expressed. Tonsils which were merely large or irregular, without injection of the pillars and yielding no pus on pressure, were not termed infected.

The Heart. Neither in the histories of the patients, the physical examinations, nor the electrocardiograms were there any evidence of organic heart disease in this group of patients. This is extremely interesting because of the high incidence of the tonsillar infection, the cause of so much organic disease of the heart. Moreover, in sharp contrast to derangement of the thyroid function, in which functional cardiac disturbances are so common, symptoms of such conditions were conspicuous by their

absence. Tachycardia was not noted in the series. Only two patients complained of palpitation, slight in amount and not caused by exercise. Bradycardia was rarely encountered, even in the patients with low basal metabolic rates. This is an interesting and important point, since in thyroid failure the pulse rate usually follows the metabolic rate downward. The fact that it does not do so in pituitary failure suggests that the bradycardia in hypothyroidism is not due solely to the low metabolism, and furnishes evidence of some importance in the clinical differentiation of the two conditions.

The Blood Pressure. Hypotension was much less marked in this series than in hypothyroidism. As a rule the pressures were within or near normal limits under ordinary conditions. Those tabulated in the first section of the paper were taken under basal conditions.

Other Viscera. Only two patients in our series showed evidence of pulmonary involvement. One had a thickened pleura following pneumonia, the other had tuberculosis. No evidence of disease of the abdominal viscera was found in the entire series.

Neurological Findings. Headache was the most common neurological symptom in the group, being present in 34 per cent of the patients with more than occasional frequency. It was usually described as frontal or vertical. So-called "migraine" was not common, in contrast to the findings in thyroid failure. Of the 34 patients with headache 25, or 73 per cent, showed yellow or hazy discs and enlarged blind spots, and 32 per cent contracted visual fields, but no papilledema or other evidences of increased intracranial pressure. This close association of headache and eye changes indicate that both are due to a common cause. In the absence of papilledema or contracted visual fields pressure by the pituitary can be eliminated as a factor and the most probable explanation lies in the disturbances of nutrition, characteristic of pituitary malfunction, and their effect upon nerve tissue in general.

That the entire nervous system shows evidence of disturbed function in conditions of abnormal pituitary function is shown by the work of Cushing (2), Davidoff (40), and others, and by the further neurological findings in our series.

Parasthesias. Twenty per cent of our patients complained of numbness and tingling of the extremities—symptoms common to other diseases in which nutrition is disturbed, i. e., diabetes mellitus, and pernicious anaemia. Ten per cent showed definite sluggishness of one or more reflexes, one case showed ataxia, and one, with thyroid enlargement, exhibited a fine tremor of the hands. All these disturbances are apparently the result of imperfect nutrition of the nervous system, as no other explanation fits the facts so well.

Deafness. Deafness has not been emphasized in connection with pituitary disturbances, but 15 per cent of our patients had definite hearing loss, as determined by the audiometer. In 5 per cent, catarrhal conditions could not be eliminated as a possible cause for the deafness, but in the remaining 10 per cent no catarrhal condition could be demonstrated, and the history was typical of the progressive non-catarrhal type—so-called otosclerosis. In the light of the known relation of that disease to pregnancy, and of our knowledge of pituitary function during and after pregnancy, the question arises as to whether otosclerosis is anything more than a nutritional disturbance of the auditory apparatus, brought about by metabolic changes, for some, though by no means all, of which the pituitary may be responsible. Work on this problem is going on in our clinic at the present time and seems to offer hope of the solution of a part, at least, of this baffling problem.

Treatment. It is generally believed that pituitary substance, administered by mouth, is inert. In our experience, this is not entirely true. In ordinary doses, no effect could be demonstrated in the majority of our patients, but doses of from one to two grams (15-30 grains) produced demonstrable results in a large number of individuals. The recent work of Menninger (52), demonstrating that in certain individuals epinephrine is effective given orally, reopens the whole question as to the effectiveness of endocrine preparations thus administered. It may be that variations in the gastric secretion of individual patients account for the variations in the effect of the preparation administered (53). Work is now being undertaken in our clinic to clear up this point, and the results of treatment will be discussed more fully in a later paper.

PART III

Case Protocols

The cases have been grouped according to characteristic symptoms. Typical laboratory data are assembled in tabular form to conserve space.

TABLE XIII

Observation		Blindness		Deafness	
		Number B-70	Number B-71	Number B-130	Number B-238
Diagnosis	Anterior	−	−	−	−
	Posterior	+	+	+	+
Sex		Female	Female	Male	Female
Age	(yrs.)	25	49	53	29
Height	(cm.)	159	153	178	155
Weight	(kgm.)	37.5	63.7	62.3	48.0
Weight	Dev. (%)	−30	+29	−10	+8
Lung Volume	Dev. (%)	−28	−26	±0	−25
Basal Metabolism	Dev. (%)	−25	−12	−24	−18
Pulse	(per min.)	64	72	52	70
Blood Pressure	(mm.)	116/80	154/84	102/68	112/66
Temperature	(deg. F.)	98.4	98.0	97.8	98.2
Alveolar CO_2	(mm.)	41	41	45	40
Urine Volume	(c.c.)	1980	870	910	1370
Spec. Grav.		1.008	1.025	1.028	1.010
Albumin		+	0	0	+
Casts		+	0	+	0
Sugar		0	0	+	0
Total Nitrogen	(gms.)	4.62	20.88	12.22	5.16
Residual Nitrogen	(%)	3.1	13.1	3.6	9.2
"Urobilinogen"		0	0	+	0
Phen. Sulph. Phth.	(%)	47	61	63	89
Gal. Toler., Deviation	(%)	−75	−50	−33	−50
Non-Protein Nitrogen	(mgm.)	35	38	47	32
Uric Acid	(mgm.)	6.3	5.5	4.5	4.1
Sugar	(mgm.)	76	84	83	87
Haemoglobin	(%)	80	90	95	80
Erythrocytes	(10^6)	4.21	5.51	5.95	4.22
Leucocytes	(10^3)	5.95	7.20	6.05	6.15
Lymphocytes	(%)	45	35	40	45
Eosinophiles	(%)	5	4	2	1

BLINDNESS

CASE B-70. The patient's chief complaints were partial blindness (chiefly in the left eye), headache, amenorrhea, and mental depression. Four years ago she began to have headaches, which gradually have increased in severity and frequency, and a few months before her admission necessitated suspension of work and later admission to a hospital. The eye condition came on gradually, but during the recent period of examination there have been intense pain, photophobia, and marked further loss of vision. The mental phase has been intermittent throughout the four years and has intensified with

the present illness. The patient matured at 16; the catamenia was regular and scanty up to four years ago. The periods then became irregular with increasing interval, and ceased entirely four months ago.

Family History: Both parents died of pulmonary tuberculosis, and one sister has recently recovered from it. A brother died at seven of meningitis and hydrocephalus.

Past History: Several minor ailments and diphtheria in childhood were recorded. She had influenza four years ago. There is a history of some deafness, pain in ears and tinnitus. The use of glasses earlier gave slight relief to the headaches. She has hacking cough, with expectoration. She has always had some nausea, followed during past few months by occasional vomiting.

Physical Examination shows an under-developed, poorly nourished white female of 25. The left eye is practically blind and with some nystagmus. The lungs show dullness in the apices and fine rales.

Laboratory Summary: The patient is much under weight and her lung capacity is diminished. The basal metabolic rate is —25 per cent; the urine volume is ample, with albumin and casts both present. Protein intake is inadequate for maintenance; residual nitrogen is normal. The galactose tolerance is 75 per cent below prediction. The blood uric acid is very high, with normal non-protein nitrogen. She has a slight secondary anæmia, lymphocytosis (45 per cent) and eosinophilia (5 per cent).

Neurological Examination shows positive Romberg, normal gait, inco-ordination of upper extremities; lesion of second pair and possible eighth nerve involvement.

Eyes: The left pupil does not react to light or accommodation. The right fundus shows papilledema (1 mm.); the left, small, superficial hemorrhage on the nasal side of the disc; the discs are yellowish. The right form fields are normal, the color field contracted; on the left, only a small upper nasal field remains (see plates). The right blind spot is somewhat enlarged; the left could not be delineated. The findings indicate an intercranial growth and lesion in left optic nerve at or in front of the chiasm.

X-Ray: The sella appears to be normal. Infilteration with calcification of the left lung are evidenced.

Ears: No abnormalities are detected. The Barany test gave normal results.

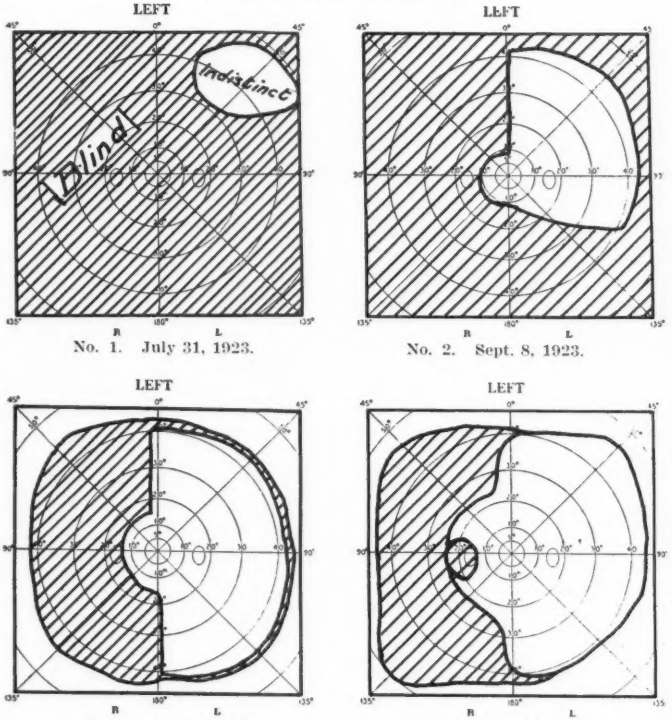
A *diagnosis* of pituitary dysfunction, with anterior lobe under- and posterior lobe over-active, coupled with pulmonary tuberculosis, was established. Because of the latter condition, operation was deemed inadvisable and anterior lobe *medication* was administered in the hope that normalizing the hypo-active portion of the gland might influence favorably the over-active fraction.

Outcome: The patient showed steady improvement and nine months later the eye findings were substantially normal (see plates) with 10/10 vision in the right and 10/12 in the left eye.

She was discharged to undergo treatment for the tuberculous condition. Three years later she reported with the pulmonary condition arrested. The eye examination showed nothing abnormal ex-

PLATE 2

Case B-70. Pituitary blindness.



No. 1. July 31, 1923. No. 2. Sept. 8, 1923.

No. 3. Dec. 13, 1923. No. 4. Feb. 20, 1924.

No. 5. May 3, 1924.

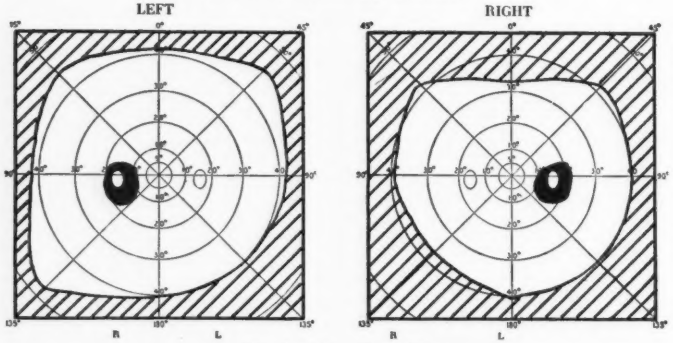
cept for persistence of the yellow discs. Her sugar tolerance had become 50 per cent above the normal, indicating a functional involution of the posterior lobe to a terminal under-active state. The patient also reported a partial resumption of the menstrual function.

CASE B-71. The patient's chief complaint was of a progressive blindness which had been first apprehended some seven months before. A diagnosis of neuro-paralytic keratitis had been made and treatment instituted, but without success.

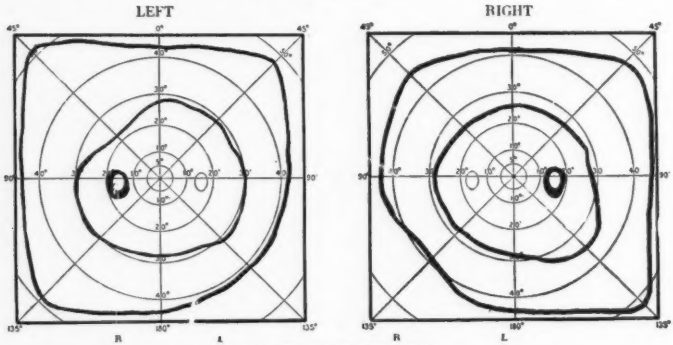
Family History: Four siblings were living and well. The father died of "growth in throat"; the mother, of old age.

PLATE 3

Case B-71. Pituitary blindness.



No. 1. Dec. 5, 1923.



No. 2. April 23, 1924.

Past History: In addition to the usual minor ailments, the patient reports scarlet fever in childhood, an appendectomy at 36, and recently the extraction of a number of teeth. She had been subject to headaches in recent years and some emotional instability. Men-

struation began at 13; the periods were regular, every 28 days, with no pain, and normal amount. Her last period was eight months earlier; she is in the menopause.

Physical Examination shows a well developed, short, white woman of 49. She is somewhat obese, with a tendency to girdle distribution. The general physical examination disclosed no other abnormalities.

Laboratory Summary: The patient was 29 per cent over weight, with slightly low basal rate (the value recorded being probably somewhat high). She showed ample protein intake, with a high residual fraction of the urine nitrogen; sugar tolerance depressed; significantly high blood uric acid; a slight relative lymphocytosis and 4 per cent eosinophilia.

X-Ray: Shows some obscuration of the left antrum, increased density of the pituitary and erosion of the posterior clinoid process; also a retained root of the left first upper bicuspid.

Eye Examination showed marked impairment of vision; cornea and vitreous humour in both eyes somewhat hazy; yellow discs; blind spots enlarged; right form field contracted, left slightly so.

Diagnosis: Pituitary dysfunction, anterior lobe under-, posterior lobe over-active.

This case was also one in which operation offered, but doubtful hope of benefit for serious risk. Medication with anterior lobe pituitary substance was instituted with definite improvement in vision, as can be shown by the accompanying figures.

TABLE XIII-a

DISTANT VISION RECORDS

Date	Right	Left
September 9, 1923.....	20/500	20/150
December 5.....	20/1000	20/150
January 2, 1924.....	20/200	20/80
February 27.....	20/150	20/40
April 23.....	20/80	20/40

The fields became practically normal and there was distinct reduction in the size of the blind spots (see plates).

The improvement here noted was probably due, in part at least, to an improvement in metabolism resulting from the glandular correction. In the supervening years there has been some loss of acuity, but the progress has been slow and the present status much superior to that at the initial contact.

DEAFNESS

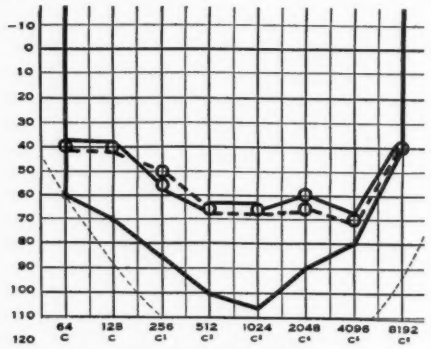
CASE B-238. The patient's complaint is of a bilateral loss of hearing. Eight years ago she had several severe sore-throats, to correct which a tonsillectomy was performed. The deafness, which was remarked just prior to the operation, has been progressive to the present.

Family History was not significant, except for two maternal uncles, who were both deaf following abscessed ears in childhood, and a brother who is also somewhat hard of hearing.

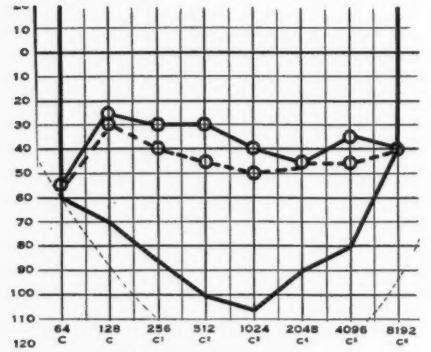
Past History: The patient had the usual children's diseases; an appendectomy one year ago; a laparotomy three years ago for unknown cause. She has had several breast abscesses. She has been married six years, has had no children, but three miscarriages, the most recent being eight months ago and following a long automobile ride, The catamenia began at 16; the periods have been irregular and have not resumed since her last miscarriage. There have been attacks of vertigo during the past six months, but no headaches. She has lost forty pounds in past few years, having dieted rigorously for obesity.

PLATE 4

Case B-238. Pituitary disease with deafness (otosclerosis).



No. 1. Dec. 30, 1924.



No. 2. Aug. 5, 1925.

Physical Examination showed a well developed and nourished white woman of 49. Beyond a partial nasal obstruction and her deafness the examination disclosed no abnormalities.

Laboratory Summary: With a sitting height index of 0.51, the patient is 8 per cent above her predicted weight. This indicates that

at the height of her obesity (v. s.) she was nearly 50 per cent overweight. The basal metabolic rate is low; the blood pressure somewhat below normal. The urine shows albumin; its composition indicates a low protein intake; the residual nitrogen is slightly high. Her sugar tolerance is but half the normal. The blood uric acid is high. There is a slight secondary anæmia and the blood is lymphoid in type.

Eye Examination shows yellow discs, enlarged blind spots, some temporal cutting of the right form field, and some contraction of both color fields.

Neurological Examination affords no evidence of organic disease. It defines a social problem which seemingly does not contribute to the present condition.

X-rays of skull, sella, heart and lungs show no abnormalities.

Barany is normal.

Pelvic examination shows normal structures.

Ear examination showed no organic defect.

Audiogram (see plate) demonstrated a marked loss of hearing.

Diagnosis and Outcome: On the basis of the general picture, reenforced by the eye findings, a diagnosis of pituitary dysfunction with the anterior lobe under- and posterior over-active was established, and anterior lobe medication begun. The deafness gradually improved, as is shown in the audiogram (see plate) taken eight months later.

CASE B-130: The patient's chief complaint was of deafness, first noted some eight years ago and progressive since that time, though no great change has been noted in the past two years. Forty years before he had had a discharging ear, which soon cleared up and did not seem to affect the hearing. At the onset of the present condition there had been much tinnitus, but less in the past few years.

Family History showed a distinct tendency to circulatory disease, but otherwise was not remarkable.

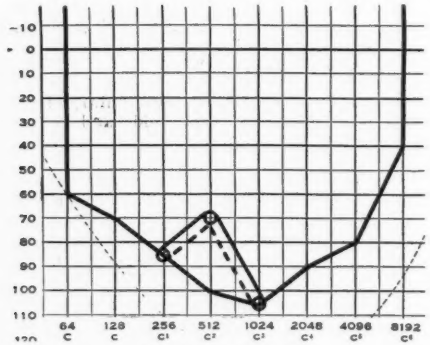
Past History: In addition to the diseases of childhood there is a history of neuritis in the neck; trauma to the head 19 years before with concussion; complete recovery in a week. Gonorrhea was contracted 20 years before, but apparently complete recovery took place. There has been some headache, occasional vertigo, and at one time frequent epistaxis. He has been married nine years; his wife has had several miscarriages and one child which died shortly after birth.

Physical Examination shows a well developed, fairly well nourished white male of 53. with somewhat doubtful teeth. Except for this and a minor cervical and inguinal adenopathy, the physicial examination disclosed no abnormalities. At the time of the examination the patient was unable to receive communication except in writing.

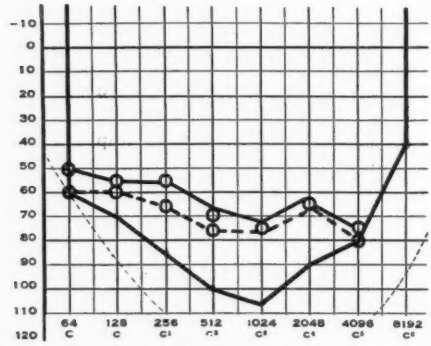
Laboratory Summary: The patient is 10 per cent underweight; the basal rate is low (—24 per cent), as is the pulse rate and the blood pressure. The urine shows casts and sugar. The protein intake is adequate; the partition formula, normal. The "urobilinogen" test is positive. Sugar tolerance is depressed. The nitrogen content of blood including the uric acid is increased. There is relative lymphocytosis. The serological tests were negative.

PLATE 5

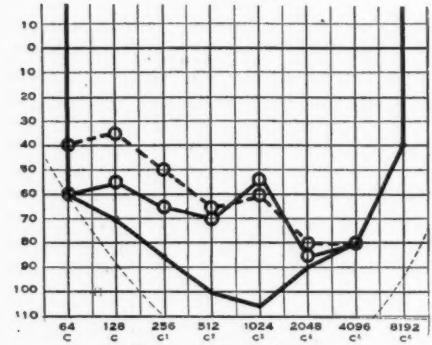
Case B-130. Pituitary disease with deafness.



No. 1. May 19, 1924.



No. 2. Dec. 19, 1924.



No. 3. Mar., 1928.

Ear Examination: The internal ears showed normal function. Some degree of stiffening of the drum heads and ossicles from chronic otitis media was noted.

Neurological Examination gave normal findings.

X-Ray showed sinusitis of frontals, ethmoid and antrum.

Eye Examination showed yellow discs, somewhat enlarged blind spots, and some cutting of the upper fields due to heavy, overhanging eyebrows.

The audiogram showed complete loss of hearing, except at 512 cycles, where there was slight residual acuity (see plates).

Diagnosis: The patient presented a definite sinusitis, gave evidence of lowered kidney permeability, a history in some respects suggestive of a specific eighth nerve involvement, but denied by several negative serological examinations. In addition, there was a suggestion of possible pituitary dysfunction of the common type (anterior lobe under-, posterior, over-active.

Outcome: He was given a therapeutic test with anterior lobe medication. In six months his hearing had improved markedly (see plate); he was able to understand conversation, and this condition has persisted, with possibly slight improvement in the speech area (see plate) up to the present time. Later incomplete examinations have shown a marked improvement in the laboratory picture, including a disappearance of the glycosuria.

ASTHENIA

The next group to be considered is that in which asthenia was the principal difficulty. Cases have been selected illustrating two types, hypo- and dys-functional disorder of the pituitary. The laboratory data are given in the next table, as are those for two cases of headache.

CASE B-28. This patient was studied in the early days of these investigations and the records lack something of the completeness of the later reports. His chief complaint was of a marked fatigability, a slowing down and blunting of the mental processes, and ocular disturbances of a variable and intermittent character (v. i.). He had left college to accept a commission at the time of our entry into the war, served in the A. E. F., and after demobilization had resumed his interrupted studies. When first seen he was experiencing difficulty in completing a very elaborate academic program in which he had been engaged for several years.

Family History: Beyond a younger brother, who presented a retarded mental and physical development, the family history reported no abnormal individuals.

Past History: The patient reported the minor ailments of childhood, but gave a history of general good health and successful athletic activity until he entered the Army. He grew rapidly at or about the time of puberty and attained his height of six feet five inches while still a youth. During his army experience in France he devel-

oped a defect of vision, which was later shown to be due to a choroidal hemorrhage, producing a scotoma. After his discharge, as above stated, he resumed his studies and the remaining history was uneventful, except for the gradually progressive loss of physical and mental endurance.

TABLE XIV

		Asthenia		Headache	
		Number B-28	Number B-160	Number B-127	Number B-186
Diagnosis	Anterior Lobe	−	−	−	+
	Posterior Lobe	−	+	+	+
Sex		Male	Male	Male	Female
Age	(yrs.)	27	38	29	31
Height	(cm.)	195	183	163	170
Weight	(kgm.)	86.5	66.0	52.0	65.1
Weight	Dev. (%)	−4	−14	−7	+1
Lung Volume	Dev. (%)	+18	−24	−11	−31
Basal Metabolism	Dev. (%)	−13	−7*	−15	+18†
Pulse	(per min.)	56	72	57	74
Blood Pressure	(mm.)	118/64	120/82	102/64	124/84
Temperature	(deg. F.)	97.1	97.2	97.4	98.6
Alveolar CO_2	(mm.)	55	44	**33**	−
Urine Volume	(c.c.)	2250	1360	1430	2000
Spec. Grav.		1.013	1.017	1.015	1.012
Albumin		0	0	+	+
Casts		0	0	0	0
Sugar		0	0	+	0
Total Nitrogen	(gms.)	13.48	10.92	11.16	13.46
Residual Nitrogen	(%)	2.7	3.5	6.9	5.1
"Urobilinogen"		+	+	0	0
Phen. Sulph. Phth		90	56	67	36
Galactose Tolerance	Dev. (%)	+67	−67	−67	−50
Non-Protein Nitrogen	(mgm.)	31	42	36	37
Uric Acid	(mgm.)	4.9	4.8	4.2	3.0
Sugar	(mgm.)	88	104	73	86
Haemoglobin	(%)	95	95	95	100
Erythrocytes	(10^6)	5.19	5.17	5.08	5.30
Leucocytes	(10^3)	7.50	5.70	6.90	6.40
Lymphocytes	(%)	31	36	22	36
Eosinophiles	(%)	0	5	4	0

* Not basal. Patient slightly restless.
† Slightly earlier test showed +40%, but patient nervous and test not basal.

Physical Examination: The patient was a symmetrically developed white male athlete, twenty-seven years of age. The face was the so-called pituitary type, the hands and feet large and well formed, the fingers long and tapering (type "en longe"). His general examination gave no abnormal findings, except for the eye condition to be discussed below, and a few minor varicosities in the lower limbs. This latter is a somewhat characteristic pituitary finding.

Laboratory Summary: His weight was but 4 per cent below prediction, his lung capacity 18 per cent above the most exacting (athlete) standard. The basal rate is below normal (the value —13 per cent is probably not exact, —20 per cent, obtained a few days

later, being more nearly basal); the pulse is slow. The urine was normal, save for a positive test for "urobilinogen." The sugar tolerance was much above the normal; the blood uric acid high; the blood morphology substantially normal.

X-Rays showed a normal sella and large frontal sinuses.

Barany tests showed intact and normally functioning labyrinths, with nystagmus unusually small in amplitude.

Eye Examination showed yellow discs, enlarged blind spots, and fields which were normal except where influenced by the scotoma. There was an absolute scotoma in the left side of the right field; a large absolute scotoma in the left field. In addition, there were several "moth eaten" areas in both eyes, due to degenerative changes in the retina and underlying choroid.

Diagnosis: The above picture defines a present bilobar hypofunction of the pituitary. The patient's physical habitus makes it seem probable that there was an early hyperactive phase at puberty, at least of the anterior lobe, which had spontaneously arrested.

Outcome: Medication with the components of the whole pituitary gland produced a marked improvement in the clinical picture, and he was able, not only to complete his academic program successfully, but to resume his athletic activities and row on a successful varsity crew. The eye condition has remained unchanged, the initial damage being permanent in its results.

CASE B-160. The patient's *Chief Complaint* was of marked asthenia, accompanied by severe supraorbital headaches. These were frequently associated with nausea and vomiting, relief following the latter. They came originally at monthly intervals, latterly every week or ten days. The whole condition was of some fifteen years' duration.

The *Family History* was not relevant, except for one sister, who died of diabetes.

His own Past History was almost equally negative. He had severe pneumonia at the age of two, and a temporary (?) cardiac disturbance, seemingly following severe influenza at the time of the epidemic. Beyond these, he has had no serious illnesses, but has never been robust. He has been married ten years; his wife has borne two children; she has had no miscarriages.

The *Physical Examination* showed heart and lungs normal; teeth show much dentistry; there is a minor inguinal adenopathy. The patient is six feet tall, a fairly well developed and nourished white male of thirty-eight.

Laboratory Summary: He is somewhat underweight and below his predicted lung volume. The basal rate is below normal (see table foot note); the urine gives a positive "urobilincgen" test; his sugar tolerance is markedly low; the blood uric acid is high, but the nonprotein nitrogen is also somewhat above normal. The blood shows a slight relative lymphocytosis and 5 per cent eosinophilia.

X-Ray shows normal skull, sella and heart, some pulmonary fibrosis, and a single infected tooth.

Neurological Examination showed no abnormalities except a slight quantitative difference in the reflexes of the lower extremities.

The *Audiogram* showed slight but definite impairment of hearing (17 per cent).

Eye Examination recorded yellow discs, slight blind spot enlargement, and somewhat contracted fields.

Diagnosis:—The picture as given above defines a pituitary dysfunction with the characteristic formula.

Outcome: On the basis of this diagnosis anterior lobe *medication* was prescribed. The patient reported ten months later that his general level of endurance was practically normal, that he had had five months' freedom from headache, and in the remaining interval an occasional and not severe headache. A brief laboratory examination showed a normal basal rate, blood chemistry and morphology; no change in the audiogram, and practically normal eye findings.

HEADACHE

CASE B-127. The patient originally came to the hospital with what was apparently an attack of renal colic. Physical examination, x-ray and other observations failed to substantiate the diagnosis, and the condition cleared up spontaneously during his hospital residence. He was transferred to us from the Surgical Service, as radiography showed a skull configuration suggesting acromegaly.

The present complaint is of headaches which began three years ago. Originally they were intermittent and relatively infrequent, but for some months past they have increased significantly in frequency and severity. They come over the right eye, but usually involve the whole frontal region, but do not radiate from this area. They are not associated with visual or gastric disturbances.

Family History: The patient was born in Russia and came to this country as a youth. He knows nothing of his family history except that he has five siblings living and well in this country.

Past History: The significant features are an earlier hospital admission for diabetes (undoubtedly a pituitary glycosuria); congenital (?) absence of a sense of smell; marked irregularity of the bowels, the usual interval being three or four days (seemingly a physiological peculiarity); some loss of hair from the vertex, but not from other parts.

Physical Examination: The patient is a well developed, slender white male of twenty-nine. The face and skull are markedly asymmetric with protruding, prognathous lower jaw. Some loss of hair over the ears is noted. The remaining findings are substantially normal.

Laboratory Summary: He is 7 per cent underweight; the basal rate is below normal; the pulse, blood pressure and temperature are moderately reduced; the urine shows sugar and albumin, but is otherwise normal, as is the nitrogen partition; sugar tolerance is much depressed; blood uric acid is high, and a leucoid blood with 4 per cent eosinophilia is present.

Neurological Examination gives substantially normal findings.

Eye Examination shows yellow discs, enlarged blind spots, and normal fields.

The *Barany* tests are normal.

X-Rays show normal heart, lungs and hands; infected teeth; very irregular and asymmetric skull with long prognathous jaw, prominent diploic veins and large frontal sinuses. The sella is small with heavy anterior and posterior clinoids (see plate).

PLATE 6

Case B-127. Anterior-posterior x-ray of skull.

The x-ray plates would seem to indicate that the lateral asymmetry of the patient's skull was repeated in the sella with an intrasella space like a truncated cone.

Diagnosis: The patient seems to present a case of aborted acromegaly, with the pituitary, at time of observation, in the characteristic dysfunctional state.

Outcome: The patient was placed on anterior lobe *medication* and for a time showed very definite improvement in his clinical condition. His grade of intelligence was rather low and after a time he

failed to follow his medication consistently. He then acquired syphilis and passed under other care.

Case B-127. Lateral x-ray of skull.

CASE B-186. The patient's chief complaint was given as headache complicated by polyuria and irregular menstruation. The headaches began at puberty, lasted from two to twenty-four hours, and came at irregular but frequent intervals. They were located in temples and vertex. Latterly they have been accompanied by vertigo and faintness. The polyuria began at fifteen and has been progressive except for a brief interval in 1918, following the influenza. The catamenia was established at thirteen, but was very irregular (increased interval) until seventeen, when they assumed a normal rhythm up to a year ago. At this time a tonsillectomy was performed, following which the patient has had but five periods, although the flow has increased somewhat.

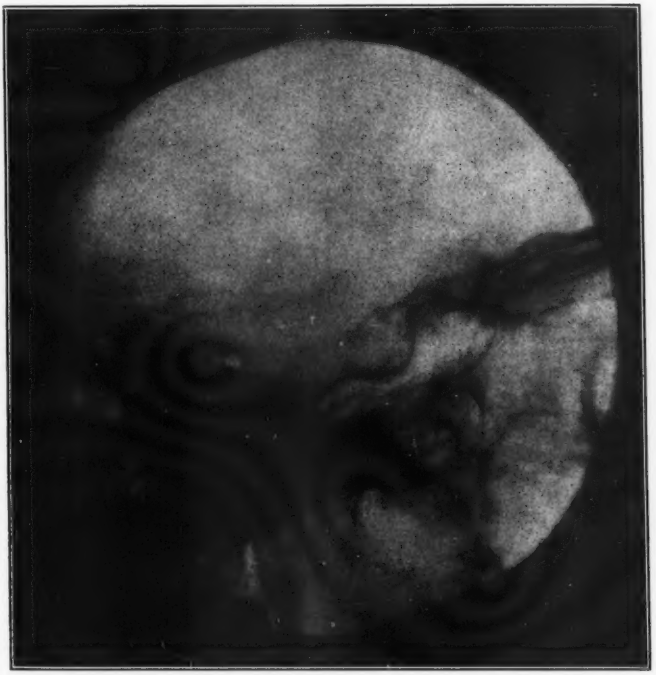
Family History: The father is reported as having been an invalid all his life, to have been a sufferer from headache. and "to have suffered from one form of diabetes as a young man." The remaining history is irrelevant.

Past History: Beyond the facts already noted, there was a probable pneumonia; an attack of rheumatism a year ago, for which the

tonsil operation was performed; at this time a swelling in the neck in the neighborhood of the thyroid appeared, which "was reduced by x-ray"; some night sweats; otherwise nothing significant.

Physical Examination: The patient was a very well developed, tall, muscular white female of 31, of a distinctly masculine type. The facies is suggestive of the characteristic acromegalic formula. There is marked hypertrichosis with tendency to masculine distribution. There is a slight strabismus in the left eye. The breasts are small. There is slight dullness over the left lung (residual from the earlier pneumonia). Otherwise the findings are normal.

PLATE 6-a



Case B-186. Hyperpituitarism. X-ray of sella.

Laboratory Summary: The basal metabolic rate is slightly above normal, the urine volume at this time ample, but not excessive, and otherwise normal except for albumin. Sugar tolerance was at half the normal level. The blood chemistry and morphology were normal.

The *Eye Examination* shows normal fundi, greatly enlarged blind spots (more in right) and significantly contracted fields.

The *Neurological Examination* gave no evidence of organic nerve disease.

A *Pelvic Examination* gave entirely normal findings.

X-Ray showed normal heart and lungs; the sella shows partial bridging of the posterior clinoids, but the cavity approximates the normal in size.

Diagnosis: On the basis of the above findings a diagnosis of bilobar hyperpituitarism was offered.

Outcome: As the condition did not seem of the utmost severity, operation was postponed and x-ray irradiation instituted.

The results of the first series of treatments can best be tabulated.

TABLE XIV-a

Date	Basal Rate	Wt. (kgm.)	Comment
December 15, 1924.....	+23%	66.0	Feels better
January 8, 1925.....	+17%	65.9	Feels better
January 15.....	+17%	65.5	Feels better
January 27.....	+11%	65.6	No more headaches
February 12.....	+16%	66.3	No more headaches
February 26.....	+ 8%	66.6	No more headaches
July 31.....	— 5%	66.1	No more headaches

After a period of practical freedom from headache there was a resumption, and treatments were again instituted, the basal rate having gone up to +20 per cent. This second series of treatments was effective, but there have been one or two further recurrences, all of which have responded to radiation. No complete studies have been made, but the eye examinations have been repeated at intervals. The latest (February 28, 1928) shows normal fields and blind spots, and the patient reports practical freedom from headache. The menstrual function has improved, though there is still some irregularity. Only the polyuria has failed to show real improvement and the patient still has intervals when she eliminates from 5,000 to 7,000 cc. daily. A possible explanation of this might lie in the persistence of an earlier damage to the mamillary bodies which is uninfluenced by the x-ray therapy.

OBESITY

The next group of patients presents some interesting cases of obesity. The third of the group (B-92) is interesting as a case presenting an inversion of the usual dysfunctional formula. Certain significant data are collected in Table XV.

CASE B-289. The patient's chief complaint was obesity. Was obese as a child, but from the ages of eleven to nineteen had gained two hundred pounds at an apparently uniform rate. This would correspond to a weight of one hundred and thirty pounds at the age of eleven. The appetite is good, but is regarded by the patient as not excessive. He consumes a great deal of candy. He never perspires, except on the feet. He shaves only once a month, but the body hair is normal. He is nervously unstable.

Family History is irrelevant, except for a great uncle said to have been very stout.

Past History: He complains of occasional frontal headache; nothing else of significance.

Physical Examination: The patient is a tall, white male of nineteen, very obese and with marked tendency to girdle distribution. He has a short, thick neck and taper fingers. The genitalia are underdeveloped. The body hair is scanty. The abdomen is very heavy and pendulous. The remaining findings are normal. (See photographs.)

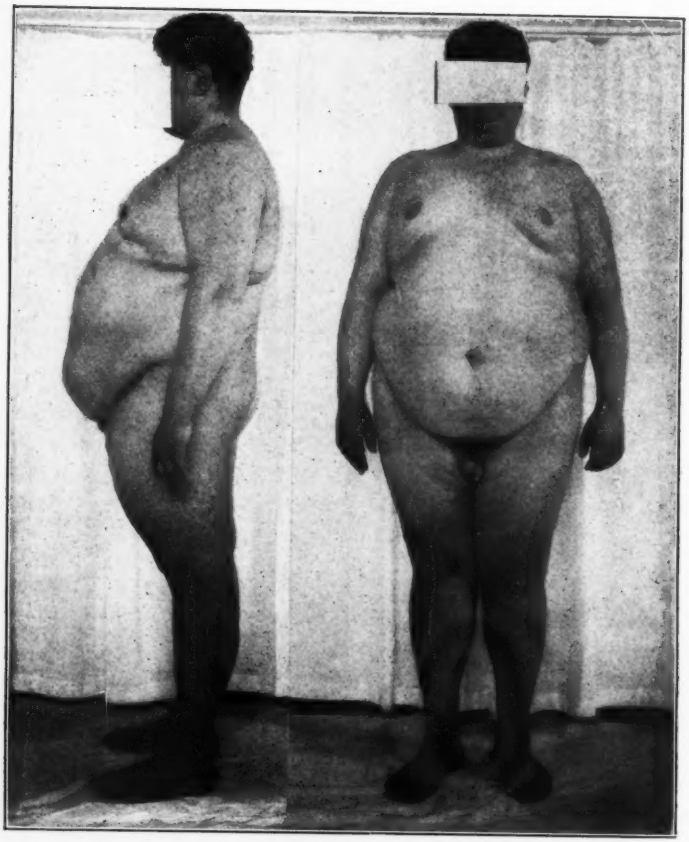
TABLE

	Obesity			
	Nunber B-289	Number C-29	Number B-92	Number B-293
Diagnosis.....Anterior.....	−	−	+	−
Posterior.....	−	+	−	+
Sex.....	Male	Male	Female	Female
Age.....	19	11	43	27
Height.....(cm.).....	177	145	156	155
Weight.....(kgms.).....	150.0	160.5	98.4	114.1
Weight.....Dev.....	+123	+215	+88	+150
Lung Volume.....Dev.....	+4	−51	−24	−14
Basal Metabolism.....Dev.....	−9	−13	+14	−19
Pulse.....	64	62	87	60
Blood Pressure.....	124/62	188/80	134/98	118/74
Temperature.....	97.8	98.6	98.0	98.4
Alveolar CO_2.....	39	46	40	42
Urine Volume.....	730	1030	620	910
Spec. Grav.....	1.030	1.026	1.018	1.020
Albumin.....	0	+	0	0
Casts.....	0	+	0	+
Sugar.....	0	0	0	+
Total Nitrogen.....	12.46	11.05	5.78	9.22
Residual Nitrogen.....	13.9	14.6	17.6	15.0
"Urobilinogen".....	0	+	+	0
Phen. Sulph. Phth.....	42	46	68	47
Galactose Tolerance.....Dev.....	+100	−33	+50	−50
Non-Protein Nitrogen.....	40	30	30	35
Uric Acid.....	4.9	5.2	4.4	4.3
Sugar.....	95	81	109	106
Haemoglobin.....	95	100	100	90
Erythrocytes.....(10^6).....	4.88	4.80	5.53	6.74
Leucocytes.....(10^3).....	5.90	8.40	10.70	7.30
Lymphocytes.....(%).....	42	36	27	34
Eosinophiles.....(%).....	2	3	2	2

Laboratory Summary: The patient is 123 per cent overweight. His basal metabolic rate is slightly low. The residual nitrogen is high. His sugar tolerance is twice the normal; the blood uric acid is high; the blood is lymphoid in type.

X-Ray shows undeveloped frontal sinuses, shallow sella, normal heart and lungs.

PLATE 7



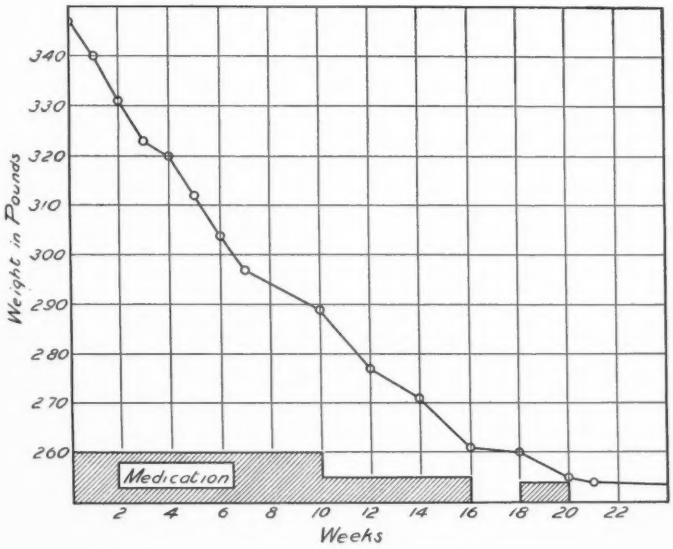
Case B-289.

Neurological Examination shows no abnormalities.

Eyes show yellowish discs, slight blind spot enlargement, and very slight form field contraction.

Diagnosis: The findings indicate a bilobar pituitary failure.

Outcome: The patient was placed on the appropriate *medication* after an interval in which his weight increased to 347 pounds. With some dietary restriction and glandular therapy, the weight loss progressed as shown in the accompanying graph. It will be noted that with suspension of medication the loss of weight stopped. After the twentieth week he discontinued the medication, and at the end of thirty-one weeks (not shown on the chart) he had begun to gain. His weight at this time was 258 pounds.



Case B-289. Change of weight with pituitary medication.

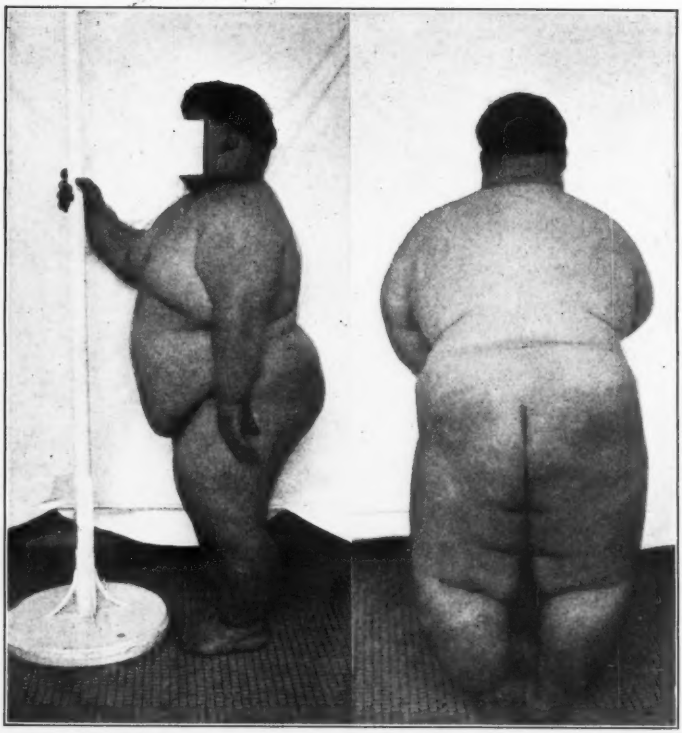
CASE C-11, 29, 37, 39. The patient's chief complaint was obesity. At the time of first contact he weighed about 165 kgm. and was 145 cm. tall. He weighed 3.8 kgm. at birth, but began to grow fat at once, so that at six months he weighed 27 kgm. Some time elapsed between his first contact and the first examination; his weight on first admission was 163.5 kgm. A preliminary study was made in February, 1925, which was incomplete (lack of co-operation), but enough data were secured to warrant a tentative diagnosis and medication and diet were suggested. Nine months later an older brother called upon us and gave the information that nothing had been done but dietary restriction at irregular intervals. At his request the patient was

re-admitted in November, 1925, and the first complete study (C-29) carried out.

Family History: The mother weighed 200 pounds, but all other members of the family were well built and not obese. The remaining history is not relevant and is not entirely reliable.

Past History: All of the minor ailments, scarlet fever and diphtheria are reported. He had abscess on the neck requiring drainage. He complained of headaches during which the eyes are "sore." He

PLATE 8

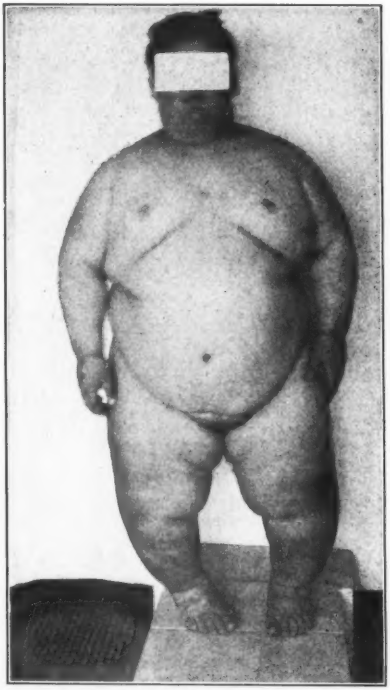


Case C-29. No. 1. No. 2.

had marked dyspnoea and palpitation; polyphagia; nocturnal enuresis; occasional incontinence in the daytime. He is easily fatigued and frequently rests by kneeling on one knee. He is of apparent average mentality.

Physical Examination: The patient was an enormously fat Italian boy of eleven. The head was very large and the fat of the

scalp could be picked up in folds. Diffuse acniform eruption and many blackheads were present. The breasts were very large. The heart and lungs were hard to define, but apparently normal. The abdomen forms a pendulous apron. But one small testicle is palpable in the large scrotum; there is seen some black pubic hair. He has small hands and feet with tapering fingers. There is maceration on all body surfaces lying in apposition (see photographs).



Case C-29. No. 3.

Laboratory Summary: The boy was 215 per cent above his predicted weight, and as his sitting-height index was 0.561 this was below the truth. The lung capacity was but one-half of prediction. His basal rate was —13 per cent (earlier figures gave a mean of —20 per cent), with high systolic blood pressure. (Independent measurements at this time indicated that the true blood pressure was about 145/80.) The urine showed albumin and casts; the residual nitrogen fraction was definitely high; the "urobilinogen" test was repeatedly positive. The sugar tolerance at this time was somewhat depressed; blood uric acid decidedly high. There was a slight lymphocytosis (?), and 3 per cent eosinophilia.

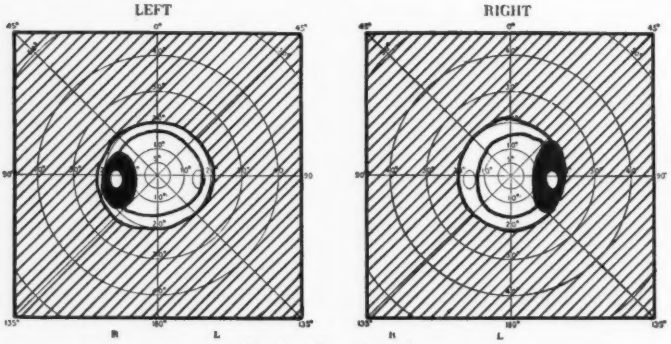
Neurological Examination showed a slowing of the mental processes without arrest of mental development.

Eye Examination showed stiff pupillary reactions, choked discs (4 diopters), very marked contraction of fields (see plate), and greatly enlarged blind spots.

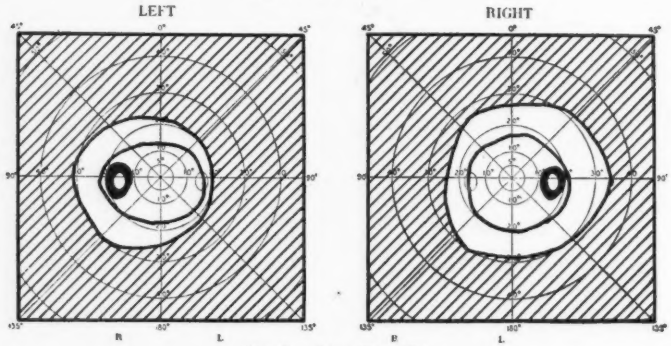
X-Ray showed infected teeth, normal sella (3 sets of plates) and thick skull wall.

A Mosenthal test of kidney function showed normal concentrating power.

An *Audiogram* showed some loss of hearing, most pronounced in the middle range.



No. 1. Nov. 5, 1925.



No. 2. June 25, 1927.

Diagnosis: A diagnosis of pituitary dysfunction with anterior lobe over- and posterior under-active was established.

Outcome: Anterior lobe *medication* with dietary restriction was prescribed. Because of the choked discs, a lumbar puncture was performed, the pressure of the fluid being in excess of 300 mm. The

laboratory examination gave normal findings. The patient was placed on Epsom salts and repeated eye examinations were made. Four weeks after the puncture the report was "practically no elevation of discs, cups clearly defined, no hemorrhage, and lymph stasis almost cleared up." During this month the patient lost eighteen pounds. After a further hospital stay, during which time medication and diet were followed, with definite weight reduction (ca. 135 kgm), the patient was discharged. He returned in May (1926) for a check up. The findings showed that neither diet nor medication had been carried out; the weight was 142.3 kgm., the basal rate —22 per cent, and the sugar tolerance unchanged. The other findings reflected the earlier therapeutic measures in more nearly normal levels. The eye findings showed no return of the choked discs; the right blind spot was smaller, the contracted fields unchanged. The parents were urged to continue the medication and diet and the boy sent home. He returned in February, 1927, giving every evidence of complete absence of any care (confirmed later by a member of the family). He had regained all of his lost weight (165.5 kgm.), the basal rate was —23 per cent, the sugar tolerance unchanged (—33 per cent). The left eye had maintained the earlier improvement; the right showed a slight return of the choked disc, but the fields were better and the blind spot smaller (see plate). Recognizing that nothing could be done for him in his home, with the consent of the parents he was placed in a state institution. They were unwilling to let him remain, however, and again took him home. The present status of the case is unknown.

CASE B-92. This case has been selected for the unusual dysfunctional formula presented.

The patient's chief complaints were obesity; unilateral deafness; palpitation and vertigo intensified at the time of her periods. The first condition was of long standing and had been gradual in its progress; the deafness followed childbearing; the other conditions date from a nervous breakdown a year earlier.

Family History: Beyond a familial tendency to tuberculosis, the history is not significant.

Past History: Minor ailments in childhood, mumps without complications in her early thirties, and a susceptibility to infections of the respiratory tract were reported. She stated that she had polydypsia and polyuria, but gave no evidence of these during hospital stay. The catamenia was established at eleven, the periods being regular and normal in amount. She has been married for a number of years and has borne three children without miscarriage.

Physical Examination: The patient was a white woman of forty-three, extremely obese and with a tendency to girdle distribution. The remaining findings were normal.

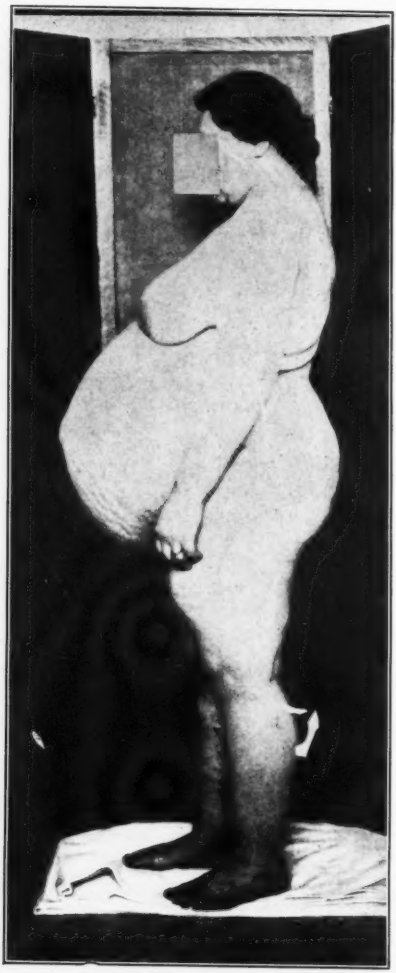
Laboratory Summary: She was 88 per cent overweight; the basal rate was slightly high (several wholly concordant observations); there were somewhat rapid pulse; urine scanty; very high residual nitrogen; positive "urobilinogen"; increased sugar tolerance; high blood uric acid; the blood morphology was normal.

Neurological Examination showed involvement of the vestibular portion of the eighth nerve. Otherwise the findings were normal.

A *Barany* test shows hypersensitivity of the labyrinth.

Ear Examination shows no anatomical changes.

PLATE 9



Case B-92.

X-Ray shows normal skull, sella, and chest.

Eye Examination shows over-filled veins in fundi, slight blind spot enlargement, and normal fields.

Diagnosis: The sugar tolerance is consistent only with a posterior lobe failure or a hypothyroidism of marked degree. This latter is denied by the basal rate. Substantiating observations are the high blood uric acid, the positive "urobilinogen," and the relatively normal levels of many of the other findings. The basal rate is on the upper side of the normal range. Coupled with the somewhat rapid pulse, it is consistent with a very slight overactivity, which is probably merging downward to an ultimate hypofunctional level. A diagnosis of pituitary dysfunction with the anterior lobe over- and posterior under-active was offered, and posterior lobe *medication* recommended.

Outcome: The patient left the state, but a year later opportunity for a partial check up showed a loss of over 20 kgm., a normal basal rate (—2 per cent), and marked clinical improvement.

CASE B-293. This case has been selected because the patient shows the most striking conformity to the conventional formula of fat distribution of the entire series (see photographs). Her chief complaint was of obesity, in addition to which she had a history of convulsions and complained of pain in the lower spine. During the first six years of her marriage she was infertile, and at the end of this period she weighed 64 kgm. In the past five years she has borne four children and had two miscarriages, with a steady increase in weight to her present level of 114 kgm. She has had two operations for the removal of abdominal fat. She stated that for the past year she has had sharp pain and tenderness in the lower spine. The convulsions started three weeks earlier. There is a preliminary sense of pressure over the left chest, and headache, followed by a gradual loss of consciousness; there ensues a tonic spasm of the body lasting no more than a minute or two and accompanied by grinding of the teeth. Several of these spasms occur during the period of unconsciousness and the attack terminates with gradual relaxation. Morphia is the only drug that has proven effective, and the patient was under a heavy morphine dosage at the time of her entrance. Seizures observed during her stay in the hospital did not conform entirely to this formula; there was prompt and complete recovery and the substitution of occult non-narcotic therapy yielded excellent results.

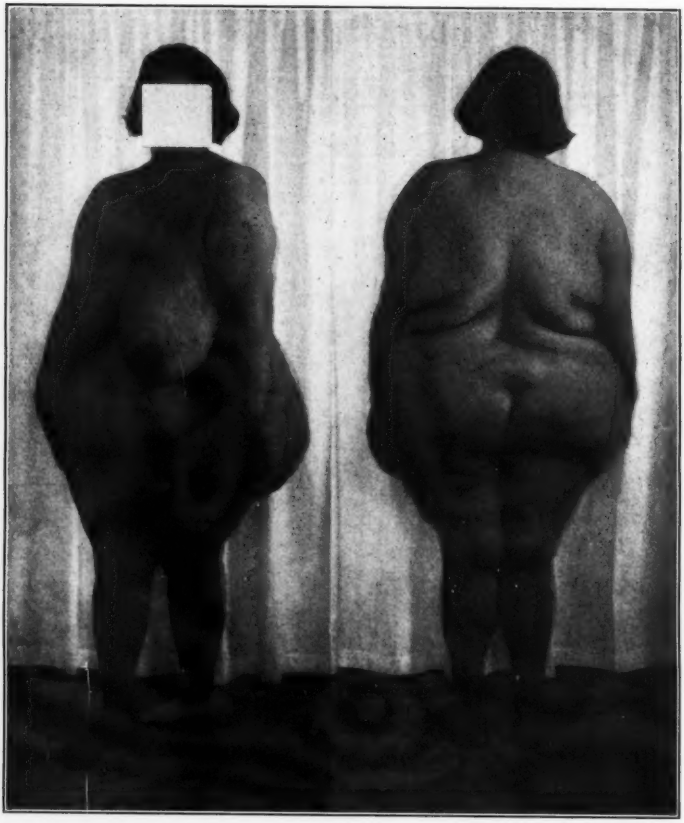
Family History is entirely irrelevant.

Past History: Beyond minor ailments and the facts stated above, the patient had four gall stone operations, the last being removal of the gall bladder. The catamenia was established at eleven and the periods were entirely normal up to the time of her five-year amenorrhea determined by her repeated pregnancies. It is interesting to note that she always conceived before the re-establishment of her periods following childbirth.

Physical Examination: The patient was a white woman of 27, with delicately moulded features, hands, feet, forearms, and lower legs, but with an enormous fat deposit in the middle third of the body. The breasts were very large and pendulous. There was a marked post-operative hernia. The remaining examination, including the spine, gave entirely normal findings.

Laboratory Summary: The patient was 150 per cent overweight, with basal rate below normal. The urine showed casts, sugar, and a high residual nitrogen fraction. The galactose tolerance was reduced to half the normal level; the blood uric acid was high; there was a slight relative lymphocytosis. A few of the patient's measurements are striking.

PLATE 10



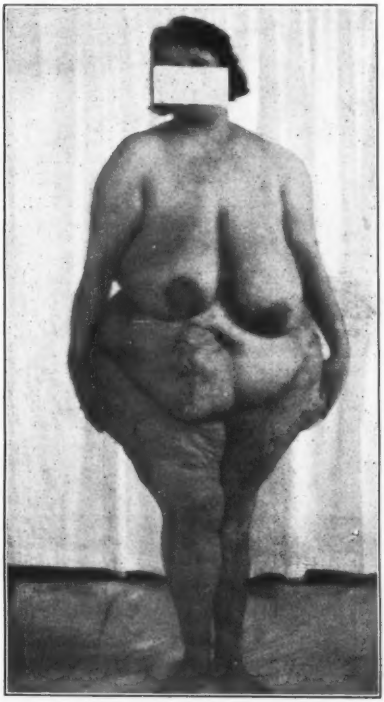
Case B-293. No. 1. No. 2.

X-Ray showed normal skull and sella.

Neurological Examination offered no evidence of organic nervous disease. The seizures were believed to be hysterical in character or possibly of toxic origin deriving from an endocrine condition.

TABLE XV-a

Chest	109 cm.	
Waist	110 cm.	
Hips	160.5 cm.	
Upper arm	Right 40	Left 42
Forearm	Right 25	Left 25
Wrist	Right 15	Left 15
Thigh	Right 81	Left 79
Calf	Right 41	Left 39
Ankle	Right 21.5	Left 20.5



Case B-293. No. 3.

Eye Examination showed yellow discs and so great a symmetrical contraction of the fields (10 degrees) that the blind spots could not be delineated.

Diagnosis: The picture given above defines a pituitary dysfunction of the usual type. Anterior lobe medication was advised, but the patient passed out of our knowledge after showing some improvement.

An interesting feature is the patient's fecundity after a six-year sterile period.

STERILITY

An interesting group of cases are those exhibiting sterility, apparently the result of pituitary malfunction, as they become fecund with the correction of the endocrine impediment. This whole question is now under extensive investigation and will be reported in detail at a later date. A single typical case is reported in the next table (Table XVI). In this table are given two series of observations on the same patient which illustrate the tendency to functional involution which this glandular structure frequently undergoes. Although a diagnosis was estab-

TABLE XVI

	Sterility	Progressive Change		Growth Arrest	
	Case No. S-260	Case No. B-162	Case No. B-162-a	Case No. B-190‡	Case No. S-1605†
Diagnosis.....Anterior...	−	−	−	−	−
Posterior...	?	+	−	N	+
Sex.....	Female	Female	Female	Male	Male
Age.....(yrs.).....	34	36	38	16	19
Height.....(cm.).....	181	160	160	132.5	150.6
Weight.....(kgm.).....	88.3	76.8	80.7	22.0	35.0
Weight Deviation....(%).....	+20	+22	+28	−34	−25
Lung Volume Dev....(%).....	−24	−24	−	−16	−24
Basal Rate Dev.....(%).....	+2*	−12*	−8*	−17	−20
Blood Pressure.....(mm.).....	134/92	112/68	106/58	90/52	96/40
Pulse.....(per min.)..	62	68	57	68	60
Temperature.....(deg. F.)...	97.4	97.5	97.9	98.1	97.8
Alveolar CO_2.....(mm.).....	35	−	−	40	40
Urine Volume.....(cc.).....	1640	2440	1450	370	410
Specific Gravity.....	1.016	1.009	1.015	1.023	1.028
Albumin.....	0	+	0	0	+
Casts.....	0	+	0	0	0
Sugar.....	0	0	0	0	0
Total Nitrogen.....(gms.).....	12.47	8.97	8.96	4.78	5.28
Residual Nitrogen....(%).....	3.8	10.1	9.3	21.8	11.0
"Urobilinogen".....	+	+	0	0	0
Phen. Sulph. Phthal...(%).....	55	32	75	30	58
Galac. Tol. Dev.....(%).....	−	−75	>+50	±0	−33
Non-Protein Nitrogen.(mgm.)....	24	39	−	29	32
Uric Acid.....(mgm.)....	5.0	2.4	3.6	2.2	2.7
Sugar.....(mgm.)....	130*	94	98	89	91
Haemoglobin.....(%).....	95	90	90	90	85
Erythrocytes.....(10^6).....	4.76	5.31	4.91	4.66	5.00
Leucocytes.....(10^3).....	7.90	9.25	6.15	5.45	8.15
Neutrophiles.....(%).....	33	53	70	38	56
Lymphocytes.....(%).....	57	44	24	55	39
Eosinophiles.....(%).....	0	0	2	3	1
Monocytes.....(%).....	10	3	4	4	4

* Too high. Patient nervous.
† September, 1924.
‡ September, 1927.

lished during the first contact, the patient declined to undergo medication and the later series of tests were uninfluenced by any intermediate therapy.

CASE S-260. The patient's chief complaint was sterility, her six years of married life with constant exposure having failed to produce pregnancy. Her husband has been shown to be fertile.

Family History was irrelevant.

Past History: The patient records minor ailments, a period of rapid growth from eleven to fourteen, at which age she established the catamenia. This latter is not remarkable except for scanty periods and headache. She was married at twenty-eight and shortly thereafter gained thirty pounds in weight. She has been fatigable; has never had much perspiration, although she feels the heat markedly. Two years ago she was given ovarian extract which produced benefit in her general condition, but had to be discontinued, as it produced palpitation.

Physical Examination: The patient was a very tall white woman of thirty-four, with a definite "girdle" obesity. The remaining findings were normal.

Laboratory Summary: The report is incomplete, since full cooperation could not be secured. She was 20 per cent overweight. The basal rate was not satisfactorily determined, but undoubtedly below the normal level. The urine was practically normal, except for a positive "urobilinogen." She had high blood uric acid and markedly lymphoid blood. The sugar tolerance could not be determined.

X-Ray showed bony bridging of the sella.

Eye Examination showed yellow discs, slightly enlarged blind spots, and a contraction of the red fields.

Diagnosis: Recognizing the numerous omissions from the diagnostic picture, a tentative diagnosis of pituitary disease was based on the available information. The anterior lobe was construed to be underactive; the posterior was undetermined.

Outcome: The patient was placed on anterior lobe *medication* and inside of three months became pregnant, ultimately delivering a normal child.

CASE B-162, 162-a. This case is presented as showing the natural course of a pituitary disorder uncomplicated by glandular therapy. The patient was first seen in May, 1924.

Her chief complaints were of some frontal headache, fatigue and gastro-intestinal disturbance. She dates the onset from an operation for the removal of a tube and ovary, the other uterine adnexa having been removed eighteen years previously. As a matter of fact, while a laparotomy was performed, the ovary was not removed and the patient has continued to menstruate up to the present, a fact that seemingly has not appeared to her to be inconsistent with her supposed condition. The headaches originated in the frontal region and radiated backward. They were chiefly associated with her periods. The fatigue was continuous and unrelieved by eighteen hours' continuous sleep in which she frequently indulged. She had frequent

attacks of excessive perspiration; there were frequent attacks of nausea and vomiting, which began after her first pelvic operation (18 years ago). In the last three years there have been intermittent attacks of diarrhoea. In addition, there were numerous minor complaints.

Family History: Completely irrelevant.

Past History: The patient had scarlet fever and several minor ailments in childhood. Nine years ago she was in bed for sixteen weeks with an attack which began with headache, vomiting, and fever, caused complete paralysis of the lower limbs and from which she recovered completely. She weighed 53 kgm. at thirty-two, and at the time of this study, four years later, 76.8 kgm. In addition to those given above, she had some operation on the bladder fourteen years ago. She had chronic cough from the age of nine. She matured at twelve years, the first period following a dilation. Menstruation was irregular with shortened interval to eighteen; since then it has been regular at twenty-day intervals with five-day periods. She has been married eighteen years with three pregnancies, resulting in one premature birth, one miscarriage, and one full term, normal child.

Physical Examination: The patient was a well developed white female of thirty-six, obese and with marked tendency to girdle distribution. The teeth were very poor; lungs normal. Some varicosities were noted in the lower limbs. Neurological and other findings were normal.

Laboratory Summary: The patient was 24 per cent overweight. On account of nervousness, a satisfactory basal rate determination could not be secured; the observed value was below the normal level. There were moderate reductions in the physical measurements; high urine volume; albumin and casts present; high residual nitrogen; positive "urobilinogen"; galactose tolerance greatly reduced; phthalein test low. The blood morphology showed lymphocytosis and 3 per cent eosinophilia.

X-Ray showed normal skull and sella and obscured frontal sinus. There was evidence of healed and calcified lymph nodes at the left apex and a calcified gland in left hilus.

Pelvic Examination showed an intraligamentous cyst in the right vault, but otherwise no abnormalities.

Eye Examination showed marked symmetical contraction of fields and enlarged blind spots.

Diagnosis: This general picture was felt to define a pituitary dysfunction of characteristic formula.

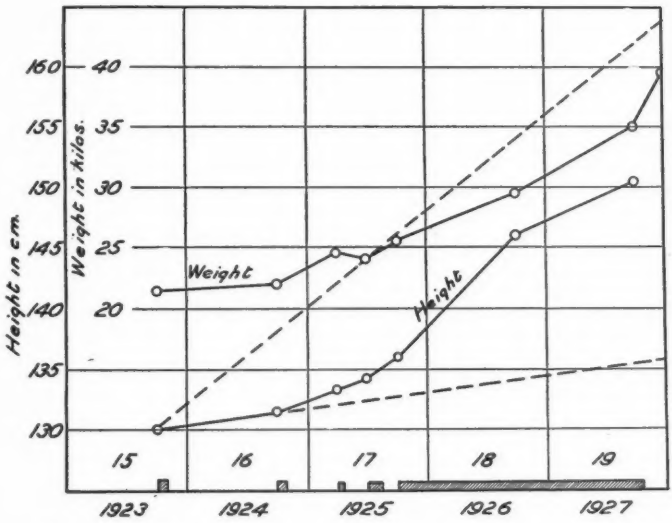
Outcome: Anterior lobe *medication* was advised. The patient declined treatment, however, but returned in January, 1926. A partial study was carried out. She had gained some 4 kgm. in weight; again a satisfactory basal rate determination could not be secured, but the observed value left no doubt as to the hypofunctional level of the anterior lobe. The complementary physical findings were slightly lower (temperature excepted); the earlier kidney condition had apparently cleared up entirely, her sugar tolerance had increased to a level over 50 per cent above the normal (she would not complete this test), the blood uric acid was relatively higher, but still normal; the blood had become leucoid in type, with a 4 per cent eosinophilia. The

eyes showed further contraction of the fields and enlargement of the blind spots. X-ray findings were unchanged. The general condition was unchanged.

Obviously, the posterior lobe had undergone functional involution during the interim, and the patient had become a bilobar failure. Appropriate medication was recommended, but contact was lost before the outcome could be ascertained.

CASE B-72, 190, C-12, Sp. 25-a-b-c, S-1605. This patient was first seen in September, 1923. A partial study was made, a tentative diagnosis of pituitary dysfunction established, and a brief course of anterior lobe medication instituted. The boy grew an inch during his hospital stay and was sent home to continue his therapy. He returned a year later. It was found that he had made no progress, and enquiry developed the fact that he had had no medicine. A complete study was made (see B-190 in Table XV) and the original diagnosis confirmed.

PLATE 11



Case B-190. Change of weight and height under influence of pituitary medication.

His chief complaint was of inability to swallow. This kept him undernourished. He was also much below the normal height for his years. He had been in good health and large for his age up to 7½ years. He then developed whooping cough and it was stated that the medicine used at this time provoked attacks of vomiting, which continued for one year. Following this, radioscopy disclosed an œsophageal stricture, and three years ago he was dilated, with temporary relief. His difficulty in swallowing is intermittent; at times solids can be taken and at others, even liquids cannot be swallowed. From

the time of the whooping cough he grew very slowly, so that he was much undersize for his age. He was referred to us for his dwarfism and for an apparently persistent thymus, disclosed by the x-ray.

Family History was irrelevant.

Past History: Beyond the facts recorded above, there is little of importance.

Physical Examination: The patient was a white boy of sixteen, greatly undernourished and looking like a child of eight. His mental age corresponded to his actual years. The head was disproportionately large. The testes were descended but very small. The genitalia were infantile in type. Beyond a minor cervical adenopathy nothing of importance was observed.

Laboratory Summary: The patient was 34 per cent underweight, with normal sitting height index. The basal rate was 17 per cent below prediction; blood pressure low; respiration somewhat slow. The urine showed poor elimination, but this was undoubtedly due to his low intake. Protein intake was inadequate and the residual nitrogen fraction was very high. The phthalein test was distinctly low. The sugar tolerance at this time was normal; the blood chemistry normal; the blood morphology showed a marked lymphocytosis and 3 per cent eosinophilia.

X-Ray examination showed a substernal shadow to the right of the spinal border; undeveloped carpal scaphoid; an unformed trochlear process of the lower end of the humerus; unformed olecranon; normal skull and sella; cardiospasm—obstruction to barium meal at cardia.

Eye Examinations showed stiff pupillary reflexes, the other findings being substantially normal.

Diagnosis: The genital arrest, the retarded ossification, the dwarfism, and the persistent thymus, all pointed to a developmental arrest. His symmetry and good proportion coupled with the laboratory findings pointed to a pituitary dysfunction in which the anterior lobe was underactive and the posterior, normal, at the time of observation. As there exists no satisfactory evidence of the endocrine property of the thymus—and much to deny it—it was felt that the persistence of this gland was but one more evidence of an arrest in normal developmental changes.

Outcome: Anterior lobe *medication* was again applied for a brief space and the patient discharged with the recommendation to continue it. This was not done, however, and during the succeeding year we had several contacts with the patient at each of which some anterior lobe was given to which he responded (See Graph). At the last of these, finding that his medication ceased when he left the Hospital, we arranged for a regular supply to be sent to him. During the first two years he had gained 6 cm. on an occasional brief period of pituitary (anterior lobe) medication; during the next two with more consistent therapy and in spite of presumptively lowered growth capacity, he has increased 14.6 cm. In the accompanying graph are shown the weight and growth curves over the interval. The dotted lines represent extrapolations, and naturally are devoid of real significance, but are possibly suggestive. The lower shows the predicted height at present had the growth rate of the first year persisted; the

upper, the prediction had the boy enjoyed the benefit of adequate medication from the beginning.

During 1925 the boy developed a slight general adenopathy. A biopsy was performed but the tissue removed gave no clear-cut evidence of the presence of Hodgkin's disease. The latter history would render this condition highly improbable.

Nose and Throat findings were normal.

An *Audiogram* showed a slight loss of acuity in the speech area.

He has had a complete laboratory check up at yearly intervals, the data from the latest being given in Table XVI. It will be noted that his basal rate is still below prediction, and this is due to the impossibility of grading the dosage to his needs under the conditions imposed upon us. The throat condition has cleared in large measure, but is not entirely corrected. This has determined the low nutritional intake which has undoubtedly influenced his growth curve on the one hand and his urine elimination picture on the other. The residual nitrogen fraction is approaching normal limits. The phthalein output is now normal, and indication of a better general metabolic level. The sugar indicates a present slight overactivity of the posterior lobe. This has fluctuated during the period of observation, at times being over-, at times under-active. At no time has there been an over supply of the active agents of the anterior lobe, though the degree of hypofunction has fluctuated with the medication and the patient's needs. The lymphocytosis, while still in evidence, is significantly decreased.

X-rays show a mediastinal shadow below and behind the sternal notch; the heart gives some evidence of dilation.

An *Eye Examination* gives normal findings except for yellow discs, the pupillary reflexes being entirely normal. "Urobilinogen" was noted at times in the urine but has apparently disappeared. The earlier adenopathy has largely cleared up. Clinically, the boy is greatly improved, is now in college, and doing very well.

Comment: In reviewing this case one cannot but regret that sustained controlled therapy could not have been followed from the beginning. It is idle to speculate as to results, but with those obtained by highly irregular treatment it may be assumed that the salvage would have been even greater.

EVOLVING ACROMEGALY

CASE S-326, 326-a, B-269, 269-a, 475, 475-a, 475-b, 475-c: This case has been under almost constant supervision since 1924. While it will be reported at length elsewhere in the near future and certain phases of the carbohydrate metabolism have recently been completed by one of our colleagues [Ulrich (54)] it presents certain points of such marked interest as to warrant brief presentation here. The patient is still under observation.

The patient was first seen in July, 1924; he was a powerfully built young man of twenty-four with the typical facies of acromegaly. The chief complaint was of recurrent paroxysmal headache which began in 1921 with increasing frequency and intensity during the interim.

Family History is entirely irrelevant.

Past History: Beyond a few minor ailments and a recent tonsil and adenoid operation, the history was entirely uneventful. A photograph taken in 1916 gives no evidence of acromegaly, but one at twenty, a year before the onset of symptoms, shows well marked and typical changes.

Physical Examination: The patient was a powerfully developed, well nourished white male of twenty-four. The hands were large, the feet of normal size. There was marked generally distributed pilosity. The reflexes were present but somewhat sluggish. The remaining findings were completely normal.

TABLE XVII

	July, '24	Dec., '24	Feb., '25	July, '25	Mar., '26	Dec., '26	Sept., '27
	Case No. S-326	Case No. -326-a	Case No. B-269-a	Case No. B-475	Case No. B-475-a	Case No. B-475-b	Case No. B-475-c
Diagnosis.....Anterior...	−	+	+	−	N	+	+
Posterior...	−	+	+	+	+	+	+
Sex.....	M	M	M	M	M	M	M
Age.....(yrs.)	24	25	25	25	26	27	28
Height.....(cm.)	172	172	172	172	172	172	172
Weight.....(kgm.)	83.4	81.2	82.5	87.5	80.5	77.0	69.2
Weight Deviation....(%)	+21	+19	+20	+28	+18	+8	−3
Lung Vol. Dev.....(%)	+9	+1	−2	−3	−24	−2	−21
Basal Rate Dev.....(%)	−11	+65	+12	−7	+4	+28	+54
Blood Pressure.....(mm.)	110/55	148/72	130/58	106/60	100/80	106/58	120/78
Pulse.....(per min.)	53	91	68	62	69	76	78
Temperature....(deg. F.)	97.9	97.8	98.0	97.6	98.0	97.8	98.0
Alveolar CO_2.....(mm.)	−	43	41	45	42	48	44
Urine Volume.....(cc.)	1010	7920	1950	1740	2140	1890	1540
Specific Gravity.....	1.017	1.034	1.018	1.014	1.027	1.037	1.038
Albumin.....	0	0	0	+	+	0	0
Casts.....	0	0	0	0	0	0	0
Sugar.....(gm.)	0	238	0	0	133	74	78
Total Nitrogen.....(gms.)	7.66	23.92	13.94	11.44	12.75	14.55	4.28
Residual Nitrogen....(%)	5.2	4.8	5.5	9.5	13.9	11.9	3.8
"Urobilinogen".....	0	0	+	0	0	0	0
Phen. Sulph. Phthal..(%)	46	68	46	46	43	48	44
Galac. Tol. Dev.....(%)	+33	−	−33	−67	−67	−83	−67
Non-Pro. Nitrogen(mgm.)	35	59	27	32	27	26	33
Uric Acid.....(mgm.)	5.1	6.6	3.7	4.3	3.0	4.7	2.4
Sugar.....(mgm.)	102	404	99	103	364	334	510
Haemoglobin.....(%)	100	85	80	100	100	90	98
Erythrocytes.....(10^6)	5.70	5.42	4.36	5.69	6.07	5.18	5.26
Leucocytes.....(10^3)	9.75	10.40	8.25	11.36	11.50	11.30	21.60
Neutrophiles.....(%)	47	54	46	57	52	53	67
Lymphocytes.....(%)	44	39	48	38	40	38	30
Eosinophiles.....(%)	5	6	3	2	5	2	1
Monocytes.....(%)	4	1	3	3	3	7	2

Laboratory Summary: The patient was 21 per cent overweight, with basal rate of —11 percent, blood pressure slightly low and pulse slow. The urine presented a normal picture throughout. The galactose tolerance was slightly high; the blood uric acid definitely above normal; the blood was lymphoid with a 4 percent eosinophilia.

X-Ray showed an enlarged sella with shallow, eroded floor (see plate) and large frontal sinuses.

PLATE 12

Case S-326. Before onset.

Case S-326. After onset.

The *Barany test* was normal.

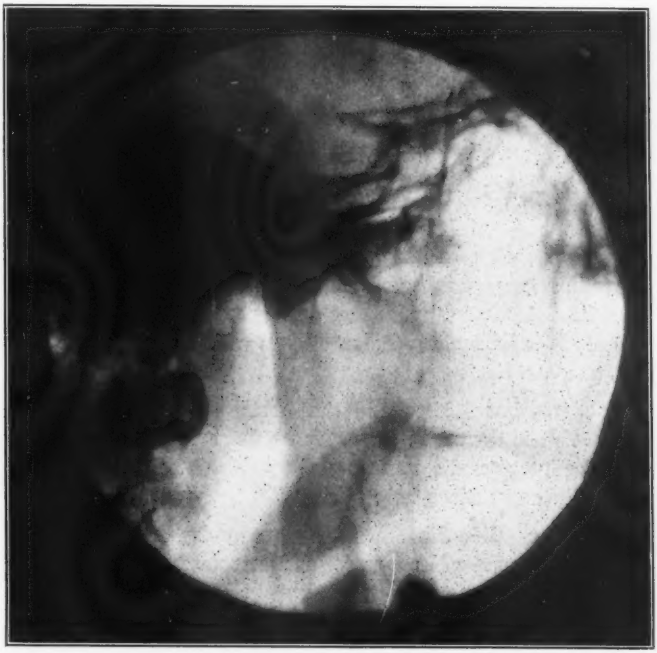
Eye Examination showed 20/60 vision in both eyes, yellow discs with indistinct margins, enlarged blind spots, normal form but contracted (left) color fields.

Diagnosis: From the picture presented the diagnosis was established as acromegaly with the gland in the final or hypo-functional state.

Case S-326. Before operation.

Outcome: As the patient was unable to work, he was retained at the hospital under observation. The condition seemed static, but in September there was a resumption of the headaches, which were very severe. After consultation it was decided to try the effect of deep x-ray irradiation, and on September 29 and October 7 treatments were given. These were followed by complete freedom from pain subsequent to the latter date. The color field showed marked improvement. Treatments were given on October 17 and 25 and November 7, there

having been but one slight headache in the interval. The patient desired to go home for Thanksgiving and was given a two-weeks' leave of absence. On his return in mid-December a laboratory check was started with the result that the first day's urine was found to be nearly eight liters and to contain 238 grams of sugar (see 326-a in Table XVII.) He was placed under active anti-diabetic treatment, the details of which are recorded elsewhere (54), and after showing a steadily rising blood sugar with massive insulin dosage, he rapidly returned to normal with full diet, no insulin, and disappearance of the glycosuria, hyperglycaemia, and polyuria. His laboratory picture in February, 1925, showed a mild bilobar overactivity, there being seemingly a recurrence of the earlier state. In June the headaches resumed; in July the anterior lobe had again become hypoactive, but the posterior overactivity had increased (see B-475). X-ray treat-



Case S-326. After operation.

ments were resumed, but the headaches increased and in October the visual disturbances reappeared. By mid-November, however, the x-ray had again apparently controlled the situation. In a few weeks this was found not to be the case, and Dr. W. J. Mixter was called in consultation. He advised operation, and through his courtesy the patient was transferred to his service at the Massachusetts General Hospital. Early in January, 1926, Dr. Mixter performed a partial

trans-sphenoidal hypophysectomy, removing a considerable portion of the posterior lobe. Early in March the patient returned to us, having made an uneventful convalescence. Another study (B-475-a) showed a normal anterior, but apparently a still hyperactive posterior fragment. The hyperglycaemia and glycosuria were found to be present. Dr. Ulrich resumed contact with the patient and carried out a series of studies on the effect of insulin, already referred to. The patient is still under observation. There has been what seems to be a progressive upward trend to the functional activity of the anterior lobe, while the posterior fragment retains its overactivity. At the time of writing (April, 1928), the patient is having a fresh study, the results of which are not yet available. It may be said in passing that the possibility of other factors having entered the case has not been overlooked, though, as they are shortly to be considered fully, they need not be discussed here.

CONCLUSION

A paper of this type cannot be briefly summarized. It may be stated that a long series of cases have been diagnosed on the basis of certain formulas established by extensive preliminary studies already discussed (1).

Specific glandular therapy administered in strict accordance with the diagnosis as established has been shown to be efficacious in a large number of patients, producing both an amelioration of the clinical symptoms and a complementary normalizing of those laboratory findings upon which, in part, the diagnosis was based.

It seems but fair to add that while the material for this presentation is drawn in largest part from earlier cases in the series, the later results confirm and substantiate in no uncertain manner the conclusions here offered.

It is impossible for the authors to render adequate thanks to the large group of colleagues and associates who have made such vital contributions to the studies here presented. To them is due a large part of the credit for whatever merit may be found in this work.

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EFFECTS OF THYROXIN INJECTIONS ON THE SUPRARENAL GLANDS OF THE MOUSE

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INTRODUCTION

The present investigation was undertaken to test the influence of an added amount of thyroid product on the histological structure of the mouse suprarenal. Beginning with the report of Magnus-Levy (1895), who first found that thyroid feeding may cause loss of weight in an animal, numerous papers have appeared recording an increase in body weight resulting from small dosage in thyroid feeding, and a decrease in body weight or a retardation in growth produced by higher dosages, the latter effect being possibly due, in the opinion of Hoskins (1916), to the toxic effect of the larger amounts.

Besides changes in body weight, other effects that have been reported include: (a) Interference with pregnancy by thyroid of probably toxic size (Gudernatsch, 1915), an effect similar to that observed by Stockard (1913) in animals treated with alcohol; (b) hypertrophy of certain organs, including the suprarenals, following thyroxin injections (Cameron and Carmichael, 1921); and (c) sex differences in the response of the suprarenals to thyroid feeding (Hoskins, 1916; Herring, 1917; Hewitt, 1920). A sex difference in the response of the suprarenals to gonadectomy has been reported by Hatai (1915).

On the histological side, Kolmer (1912) noted the degeneration and disappearance of the reticular zone of the guinea pig during pregnancy, while Masui and Tamura (1924), in a study of the reticular zone in mice, found that this disappeared in the male by forty days of age and in the female during pregnancy and old age. Further, after castration the cortex hypertrophied until it almost equaled that of the female in size, though no effect was observable following spaying. From this equalization of size of the suprarenals in gonadectomized animals the

authors conclude that "the zona reticularis is intimately related to the sex gland." Altenberger (1924) also reported hypertrophy of the cortex after castration in mice.

Tamura (1926) gives among the suprarenal changes observable in pregnancy in mice, the disappearance of the reticular zone and the hypertrophy of the zona glomerulosa, zona fasciculata and the medulla, with the appearance of a "zona gestationis" between the fascicular and reticular zones. This zona gestationis, he includes as part of the fascicular zone, though he says the cells cannot be distinguished from reticular cells in the non-pregnant animal.

In a description of the cortical zones of mice, Miller* (1927) recognizes: (a) The glomerulosa, (b) the fasciculata, (c) a circular band of flattened cells crowded together in irregular arrangement and bordered by connective tissue externally, and (d) an "X zone" (the reticular zone of Tamura and others). According to Miller, the last mentioned disappears in the male by forty days of age, and in the female in the first half of the reproductive period, after which the gland in the female resembles that of the adult male. She also confirmed the absence of any effect on the reticular zone from ovariectomy, but emphasized the effect of pregnancy in hastening the disappearance of this zone.

In short, previous investigators have found that thyroid feeding and hyperthyroidism bring about changes in body weight of laboratory animals, and also an increase in the weight and size of the suprarenals. At the same time there is hypertrophy in the heart, liver and kidneys, organs more directly concerned in increased metabolism. Other abnormal conditions, castration, thyroidectomy, starvation, excision of the anterior pituitary, all of which involve unusual metabolic states, have likewise been found to cause an hypertrophy of the suprarenals. In the mouse, the reticular zone of the suprarenals disappears with age and sex development both of which are accompanied by changing metabolic rates. In the light of these several facts, it seemed to be a matter of considerable physiological interest to ascertain what changes might come about by increasing the amount of

* The present study was suggested by Mrs. Miller, and carried out under the direction of Dr. C. H. Danforth.

available thyroxin, which is known to stimulate metabolism markedly.

MATERIALS AND METHODS

Mice, both male and female, were chosen as the experimental animals, and thyroxin, injected subcutaneously without anæsthesia, was employed as the means of supplementing the thyroid output.

Five groups of four males each, 32 or 33 days old, were selected, each group being composed of litter mates living in the same cage under identical conditions. The left suprarenal glands were removed, under ether anæsthesia, from two of each group to serve as controls in studying subsequent changes in the right glands.

For 21 days, the thyroxin was administered in the proportion of $1:10^6$ by weight, following the method of Cameron and Carmichael (1921) with white rats. A drop of 2½ per cent NaOH was used to bring the thyroxin crystals into solution, and to this was added an amount of normal saline convenient for injection, the solution being made up each day just before use to avoid oxidative changes.

One of each pair of non-operated mice in each group was injected with thyroxin, and the other, which served as control, with an equal amount of normal saline and NaOH solution without thyroxin.

For the effects of injection on females, twelve nulliparous animals from 69 to 84 days of age, with the left suprarenals removed, were injected with the thyroxin over a period of 28 days. The dosage was the same for both males and females and was chosen in the hope that the metabolism would be sufficiently increased without obscuring the results by toxic effects. While the gain in body weight ranged from 10 per cent to 107 per cent in the treated animals, as compared with 23 per cent to 90 per cent in the controls, the dosage was apparently too toxic for four of them, the three smallest and one medium-sized mouse, for they died suddenly in the first ten days. However, death may have been due to other causes than hypersusceptibility to thyroxin, though nothing was disclosed at autopsy. Schafer (1924) reported that similar deaths had occurred during the experiments of other workers with thyroid secretion.

Since the gain in weight was constant and fairly marked in most of the mice, the dosage was doubled after the second week, with no fatalities and only one resultant loss in weight among the remaining twenty animals. In the third week signs of hyperirritability appeared, which were most noticeable during the weighing, when, instead of remaining quiet, as mice usually do during routine handling, some would jump restlessly up and down in the glass beaker in which each was weighed. This would seem to indicate that the dosage employed was about the maximum compatible with the purpose of the experiment.

At the end of the experimental period, the right suprarenals were removed under the same conditions as the left. The tissues were fixed in Mueller's solution, embedded by the chloroform-paraffin method, stained with Mayer's hematoxylin and counterstained with eosin, acid fuchsin or chromotrope.

To test the matter of a compensatory hypertrophy of one gland after the removal of the other, the left suprarenals of ten other males of 32 days of age were removed, and after the lapse of the experimental time, 21 days, the right glands were removed and the size of the two compared in serial sections. Both appeared to be of the same size.

According to Miller (1927) the left gland of mice is normally slightly larger than the right. Hence there seems to have been an hypertrophy sufficient to bring the size of the right up to that of the

left in the above series. That this increase in size after left suprarenalectomy was not due to normal growth was shown by comparison of the left glands removed at 32 days of age with those of controls removed at 54 days. Any change in these controls was in the nature of a decrease, for the reticular zone in the older males had disappeared *ad interim.*

NORMAL STRUCTURE OF LEFT SUPRARENALS AT BEGINNING OF EXPERIMENT

A. Females (69 to 84 days of age). All specimens showed four zones in the cortex (Fig. 1, A): (a) The glomerulosa, (b) the fasciculata, (c) a circular zone of flattened cells, and (d) the reticularis. The intermediate flattened cell zone (c), found also in castrated mice, was included in the reticular zone by Masui and Tamura (1924), but Tamura (1926) included it with the fasciculata in his description of its changes in pregnancy.

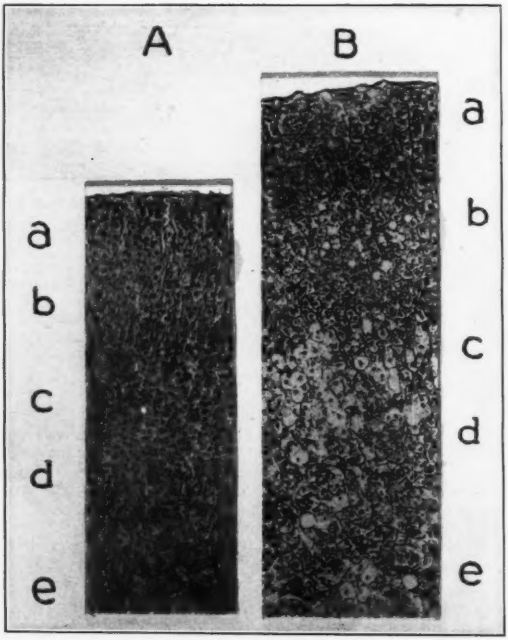

Figure 1. Suprarenals of a female showing (A) the four zones of the cortex before injection, (B) the increase in size and beginning degeneration after injections.

The figures are in pairs, showing (A) the left suprarenal gland before beginning the thyroxin injections, and (B) the right gland at the close of the experiment. a, Zona glomerulosa; b, zona fascicularis; c, the flattened cell band; d, the reticular ("X") zone; e, the medulla.

Normally, as found by Miller (1927), degenerative changes begin to take place in the reticular zone of females during the first half of the reproductive period. The first degenerative change consists of the breaking down of granules within the cells, giving a "foamy" appearance. Absorption of cell elements next takes place, leaving each cell a vacuole in itself. Neighboring vacuolated cells, from two to five, then become confluent. Large numbers of these confluent vacuolated cells form the "zona spongiosum" spoken of by Tamura. Degeneration is completed by the absorption and disappearance of these cells, a thin layer of connective tissue only being left in the place of the reticular zone.

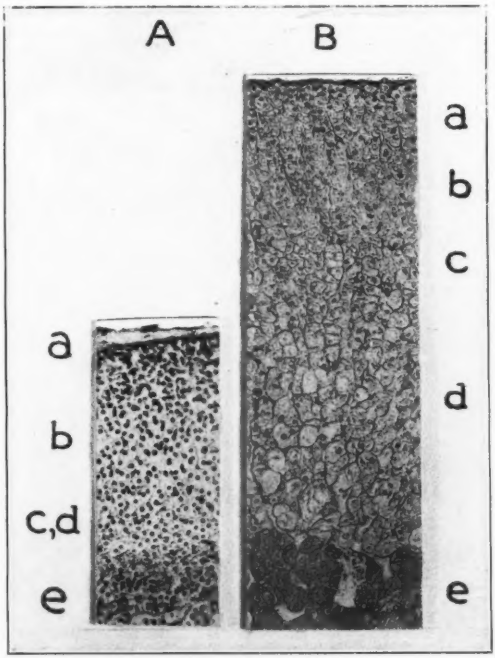

Figure 2. Similar sections from the suprarenals of a male. See legend for Figure 1.

In one-fourth of my specimens no signs of degeneration had appeared; in the rest, nine in number, degeneration had begun, though it had not progressed to the stage in which from two to six vacuolated cells become confluent.

B. Males (32 to 33 days of age). The reticular zone had entirely disappeared in one (Fig. 2, A); it was practically gone in a second; and was reduced to a narrow strip in a third; while in the other nine it was of a good width, making with the glomerulosa and fasciculata, three distinct zones.

EFFECTS OF THYROXIN INJECTIONS AFTER REMOVAL OF LEFT SUPRARENAL

A. Females (96 to 111 days of age at the close of the experiment). 1. Size of glands. An increase of 70 per cent had occurred, as measured by a micrometer along the radius of a cross section. The greatest part of the increase was due to the expansion of the reticular zone. The medullary increase was 8 per cent, the reticular 100 per cent, and the fascicular 13 per cent (Fig. 1, B).

2. Zonal changes. On examining the cells in a given area by the use of a micrometer, the glomerular cells were found to be somewhat larger. The increase in this zone was due almost entirely to hyperplasia. The fasciculata cells were increased in number, but not in size. The intermediate zone of flattened cells showed an increase from the original 2-3 layers to 6-12 layers, and the cells were less flattened, rather polyhedral in outline, but irregular and crowded together, as if under considerable pressure, which gave them an appearance different from those in either of the neighboring zones. In many of the glands vauolation started in this zone and in some cases was complete before much had started elsewhere, giving the appearance in section of a narrow, circular zone riddled with shot, as there was entire absorption of perceptible content with no confluence of cells. In the reticularis, great multiplication of cells had taken place, as shown by actual count, though the individual cells remained of the same size as before, with the exception of a few glands in which a relatively few degenerated cells, two or three in a group, had fused.

3. Denegeration. This, under ordinary conditions, would have progressed by 93 days of age to a maximum of vacuolation with fusion of neighboring cells and absorption (Miller, 1927). The effect of the thyroxin was to hold the stage of vacuolation almost stationary during the injection period of 28 days, and to result in an increase in the number of cells. Some of the glands had the "foamy" look mentioned by Masui and Tamura, which was regarded by them as due to liquefaction of secretory granules in the cytoplasm.

B. Males (53-54 days of age at the close of the experiment). 1. Size changes in male suprarenals after injections. Hypertrophy and hyperplasia of all cells occurred, with the exception of those of one gland which resembled that of the female after injection, *i. e.*, with little hypertrophy accompanying the hyperplasia. Increase in cortex width was noticeable by micrometric measurement in every one of the fifteen, the least increase being 66 per cent, the greatest 200 per cent, and the average 109 per cent. Also, there was an increase in the number of rows of cells in the width of the cortex in every case, the greatest being from 0 to 34 cells, with an average increase in the others of 100 per cent. The increase in length of the whole gland was determined by counting the number of sections in comparable series, the average being 50 per cent. The width of the medulla had increased on the average 32 per cent, no decrease taking place in any part of the gland (Fig. 2 B).

2. Zone changes in the male glands. The cortex became similar to that of young, growing animals. In one-third of the glands the zone of cells between the fascicularis and reticularis was quite distinct, as in the females; in the others it was there, but less marked.

In the glands in which the reticular zone had entirely or practically disappeared before beginning the treatment, it had reappeared (Figs. 3, A and B). In all the others, not only had multiplication

of cells taken place in a given area, but the individual cells were larger, as if multiplication had not been sufficient to meet the new demands.

The glomerular cells were enlarged in all cases, except one in which the hyperplasia had been unusually great in all zones.

A distention of the blood vessels and increased size of cells showed in the medulla.

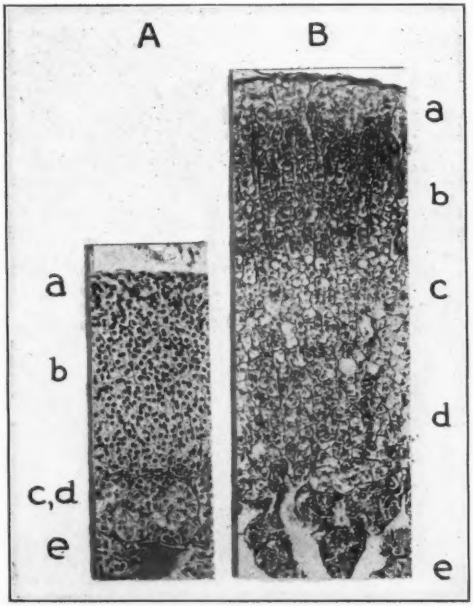

Figure 3. Suprarenals of a male. A shows only a remnant of the disappearing reticular zone. B, after thyroxin injection, shows the retention and hyperplasia of the reticular zone and subsequent degenerative changes.

3. Degeneration in the male glands. Though vacuolation does not occur normally during the disintegration of the reticular zone in the male (Miller, 1927), degenerative changes could be found in all of those injected, mostly just beyond the first stages of foamy structure and including also a few scattered vacuoles (Fig. 3, B). In several there was some absorption of contents and a little fusion of cells. In one, the vacuolation of the zone between the fascicular and reticular zones had progressed as in the females, showing the same small vacuolated cells.

THE EFFECT OF INJECTIONS ON MICE WITH BOTH SUPRARENALS INTACT

In the controls the reticular zone had disappeared entirely as it does in all normal males over forty days of age, while in the others the thyroxin had caused not only a retention and increase of the

reticular zone, but an expansion of the other zones as well. In comparing the amount of increase in the glands of the males with those of the females, allowance must be made for the apparently greater reaction to thyroxin on the part of the males, and for the fact that during the experiment the male controls had lost the reticular zone, while the injected males and the injected and control females had not. In the medullas no difference in cell size was found, but there was a greater distention of blood vessels to the glands from thyroxin treated specimens. The width of the cortex was 125 per cent greater in the thyroxin injected. The average length of the glands, as estimated from serial sections, was 600 micra greater. The average number of cells in a column of the cortex was 134 per cent greater, there being 23 additional cells in the controls and 54 in the others.

It should be noted that the total increase in these thyroxin injected animals with intact glands was twice what has been indicated, for each of the two glands increased 100 per cent by actual measurement of cross sections. Since in the operated animal the remaining gland showed only the same increase as in each of the two glands in the non-operated, it would appear that the maximum capacity for expansion had been reached in both sets of males, thus accounting for a lack of further expansion in the single gland. Very little degeneration had started in these glands by the close of the experiment.

DISCUSSION

In studying my own results and those from cognate experiments, I was struck with the fact that the zonal changes observed seem to represent a reversion to the structure of the young and growing animal in which metabolism is maintained at a higher level than in the normal mature animal, and at a much higher level than in old age. In this connection it may be of significance that the human suprarenal in the first year of life gradually loses the larger inner part of the cortex (Armour and Elliott, 1911).

The constancy with which a zone of flattened cells, which lies intermediate to the fascicular and reticular zones, enters into these histological pictures points to the possibility of its constituting an independent zone, at least in the glands of young, growing animals or in those with disturbed metabolism.

My findings with respect to body weight changes are in general agreement with the results of numerous workers with thyroid feeding. That the dosage of the thyroxin used did not cause a "definite and invariable decrease in growth," as found in rats by Cameron and Carmichael (1921), probably is due to the fact that, while the dosage was the same in reference to body weights, the metabolic rates of the two species were not taken into consideration in calculating the dosage.

The deduction of Herring (1917) from thyroid feeding of rats that enlargement of the heart, liver, adrenals, and kidneys points to a general disturbance of metabolism seems likely to me. Hoskins (1916), too, concluded that conditions increasing metabolism "naturally throw a greater burden upon important viscera and thus tend to produce in them an hypertrophy." The fact that Hatai (1915) found that increased exercise gave an increase of various organs comparable to that resulting from thyroid diet, gives color to this view. Eppinger, Falta and Rudinger (1919) also questioned whether the hypertrophy was due to the direct action of the thyroid on the suprarenals.

That hyperthyroidism stimulates the suprarenals to hyperplasia (Herring, 1920) has been confirmed in this experiment.

The flattened cell zone between the fascicular and reticular zones, found in the glands of female mice by Miller (1927), corresponds to the band which appeared in the cortex of the young males, and also in the injected females in this experiment. The description of the zone termed by Tamura the zona gestationis seems to correspond exactly to the above mentioned intermediate zone found in the suprarenals in the young nulliparous females, and also to that appearing in the glands of thyroxin injected females and in those of the young adult males treated with thyroxin. Guieysse (1901) reported that in pregnancy in the guinea pig, vacuolation begins along the inner border of the fascicular zone. This may correspond to the intermediate cell zone of the mouse.

I found that vacuolation not only often began in the intermediate cell zone, but that it was completed there, in some cases, when only a few scattered vacuolated cells had appeared elsewhere, causing this zone to stand out as a striking component of the cortex.

The changes in the suprarenals of castrated animals, shown in the plates and descriptions of Masui and Tamura, and confirmed by Miller, are similar to those brought about in young males by the injection of thyroxin. Those reported by Tamura (1926) in pregnancy, Miller (1927) regarded as normal and as merely hastened by pregnancy. These also seem to correspond to the stage of degeneration reached in the present experiments. That is, the changes in the suprarenals resulting from castration

and pregnancy appear similar in kind if not in degree to those of hyperthyroidism.

According to Macleod (1927) the histological changes brought about in the suprarenal cortex by excision of the gonads are similar to those caused by thyroidectomy and by excision of the anterior lobe of the pituitary gland. It seems probable that the results of the experiments considered in this discussion, as well as the observations of clinicians, strengthen the assumption that there is an inter-relationship between the suprarenals, thyroid, gonads and pituitary in metabolism, and that a disturbance of the balance between them brings about a compensatory increase in the suprarenals lasting perhaps until a new balance is struck.

After thyroidectomy, the load carried by the thyroid in regulating metabolism is left for other organs, just as in hyperthyroidism the co-operation of the other organs concerned with metabolism is necessary for the adjustment of metabolic changes brought about by its hypertrophy. In castration, the enlargement of the thyroid and anterior pituitary as well as the suprarenals would seem to be a similar response. Since most observers agree that the suprarenals do not enlarge in pregnancy, it would seem as if nature had made other provision in the female for taking care of the additional demands in this case. It is known that the thyroid and anterior pituitary both hypertrophy during pregnancy, which seems consistent with the fact that spaying brings about no changes in the size of the suprarenals.

Applying this conception to the present study, we find that at the beginning of the experiment both sets of animals had reached a stage in growth when the rate of body metabolism was lessening, and degeneration of the reticular zone of the suprarenals was beginning. In the controls, this degeneration continued with complete disappearance of the reticular zone, which would seem to indicate that the normal metabolic burden incident to this age can be carried without these cells and that they hence degenerate. With the great increase of metabolism brought on by the thyroxin, those with both glands were able to meet the situation by doubling the amount of tissue in them, but during the experiment the rest of the body had so far adapted itself that degeneration in the reticularis could again set in. In the group

which had lost one gland by excision, the great increase in thyroxin threw a burden on the whole organism that had to be met at once, and could not be wholly cared for by the one remaining suprarenal. Before the end of the experiment, however, this adjustment had apparently been made successfully, for degeration of the inner zone had progressed further in animals with only one suprarenal than in those that had both glands.

SUMMARY

1. The normal disappearance of the reticular zone in the male mouse after 40 days of age is confirmed.

2. Unilateral suprarenalectomy in the mouse results in dilatation of the vessels in the remaining gland, as measured in cross section, and a slight hypertrophy in 21 days.

3. (a) Daily thyroxin injections into unilaterally suprarenalectomized female mice, begun at about 70 days of age, bring about a marked hyperplasia in 28 days. The reticular zone becomes double in size.

(b) In the male, thyroxin injections begun at 32 days of age, under the same conditions, cause an increase in size and number of cells, the increase in size of cross sections being at least 40 per cent greater than that in the treated female, yet the male glands even then are smaller than those of the female.

4. The effects of thyroxin injections into male mice 32 days of age (no suprarenalectomy) stimulate a similar increase in both glands by 54 days of age, giving the non-suprarenalectomized animal twice as much cortical tissue as the suprarenalectomized and also twice that of the normal animal. A distention of blood vessels accompanies this increase.

5. A histological condition similar to that of the young, growing animal of both sexes, is produced in the male gland by injection of thyroxin. Where the normal disappearance of the reticular zone is completed, entire regeneration of the reticular zone takes place. A marked hyperemia and increased size of individual cells shows in the medulla.

In the female, all four zones have a part in the hyperplasia resulting from the injections.

6. The normal progress of degeneration of the reticular zone in the female was held almost in abeyance during the period of

treatment. Degeneration had begun in the suprarenals of all the thyroxin injected males, and had progressed least in the animals with both glands intact.

It is suggested that these glandular changes occur in response to the metabolic disturbances caused by the thyroxin, and that they are coincident with the establishment of the endocrine balance on a new level.

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THE EFFECT OF X-RAYS ON THE ADRENAL GLANDS

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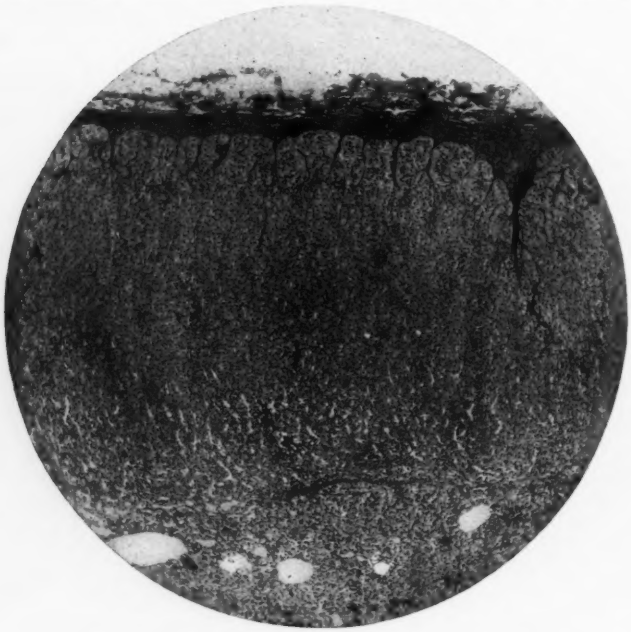
The effects of Roentgen rays on the adrenal gland as previously reported (Martin, Rogers and Fisher, 1924) are far from conclusive. Some destruction was produced but never to such a degree that one would expect symptoms of adrenal insufficiency to appear. In order to produce complete destruction of the adrenals it was decided to give larger doses and also to observe the animals for comparatively long periods of time following radiation. Stewart (1921) in his review of the literature stated that many of the conclusions regarding adrenal insufficiency were not warranted because of lack of proper evidence.

Incidentally, we thought it would be an excellent opportunity to observe the cholesterol of the blood. The relation of the adrenals to cholesterol metabolism has long been a matter of conjecture. After the removal of one gland Joelson and Shorr (1924) state that there is a hypercholesterolemia which is most marked two weeks after the operation. These investigators feel certain that there is a relationship between cholesterol metabolism and the suprarenals. The work of Randles and Knudson (1925) indicates that the adrenals do not produce cholesterol. Lucas (1926) found no appreciable change in the blood cholesterol following adrenalectomy.

METHOD

The method of preparing the animals for radiation was essentially the same as that previously described (Martin, Rogers and Fisher, 1924). For these experiments we used a cylinder 6½ in. long and 2 in. wide, in order to exclude surrounding tissues as far as possible. After the cylinder was placed over the adrenal a careful examination was made to be sure that the

entire gland was included. Then the filter was inserted. The animals were kept under deep anesthesia. Ether was given every 4 to 10 minutes as indicated by the depth of respiration. At no time did any of the animals change position during the time of radiation. When the desired dose had been administered, the filter was removed and the adrenal examined to ascertain whether the relation of the adrenal to the cylinder had been changed. In no instance was there a change of position



Normal adrenal of a dog. The three layers of the cortex and the well demarcated medulla with distinct blood vessels can be easily distinguished.

of the cylinder during radiation. The exposures were made by a 10-inch Standard X-Ray Transformer with a limited capacity setting. Under the treatment conditions of 140 KV., 5 MA., 2 mm. aluminum filter, 11-inch distance, the x-ray output was 65 R. per minute (40 R. of the German Bureau of Standards). About 6 minutes exposure represented a human erythema dose. By this method, the surface of the suprarenal gland received

390 R. primary rays. The secondary radiation was not measured, but on account of the size of the radiated region and the exposed object, this was evidently very little. The decrease of the intensity of the radiation within the object due to divergency and absorption is very limited on account of the thinness of the suprarenal gland and can be disregarded.

The right adrenal was removed from each of 4 dogs. After 2 to 5 weeks the left adrenal was given 3 to 5 erythema doses.

Adrenal of the dog exposed to five erythema doses. The thickening of capsule, the slight change of zona glomerulosa, the decided alteration of fasciculata with necrosis of cortical cells extending into the reticularis, and the medulla with thrombosed blood vessels are evident.

It was our purpose to observe these dogs for 6 months, at the end of which time a complete autopsy was to be performed and the glands studied microscopically. Three more dogs were selected to test the effects of x-rays at shorter intervals. In these three cases the preliminary operation of removing one adrenal was not performed. Four skin erythema doses were adminis-

tered to the left adrenal. One dog was killed in 3 weeks, the second in 6 weeks, and the third in 9 weeks, following the exposures. All the blood cholesterol determinations were made in duplicate according to the method of Myers and Wardell (1918). The blood samples were taken from the saphenous vein. Blood cholesterol determinations were made on the dogs before operating on them, and also following the removal of one adrenal and after radiation of the remaining gland. The dogs were kept on a liberal dog biscuit and meat diet and weighed at weekly intervals. At the conclusion of the experiment all the adrenal glands were studied microscopically as well as many of the other tissues.

RESULTS

The 3 dogs, which received 4 erythema doses over the left adrenal with the right adrenal intact, were in excellent condition when killed at the end of 3, 6, and 9 weeks, respectively. Three of the dogs from which the right adrenal was removed and later the left adrenal, received 3, 3½ and 4 erythema doses, respectively. They were in excellent condition when killed 6 months after radiation. There was no loss of weight or appetite. However, in the case of the fourth dog of the latter series from which the right adrenal was removed and the left later given approximately 5 erythema doses, there was a different response. The condensed protocol of this dog follows:

Dog B-6. Male Airedale.

2-1-26, 3:00 p. m.—Right adrenalectomy was performed.
3-10-26. The weight was 31½ lbs.
3-11-26, 2:00 p. m. The abdomen was opened. Five erythema doses were administered to the left adrenal. Operation finished at 3:00 p. m.
6-2-26. The weight was 33 lbs. The dog appeared to be in good condition.
7-30-26. The weight was 26.5 lbs.
8-19-26. The weight was 22 lbs. The dog was in poor condition. Muscular weakness was a predominant symptom. He also had diarrhea. He ate a little bread and milk. Death occurred about 9:00 p. m. Autopsy was performed at 12:30 a. m.

Some adhesions were found on the left side. The mucosa of both stomach and intestine was slightly engorged with blood. A mass of hair the size of a small fist was found in the stomach. The thyroids were very small. The lungs were in good condition. The mucosa of the gums around the canine teeth contained more black pigment than at the beginning of the experiment.

Microscopic examination. The rayed adrenal showed destructive changes in proportion to the length of radiation. The accompanying photographs show the contrast between a normal dog adrenal and one that received 5 erythema doses.

DISCUSSION

From the above results one would say that apparently no injury has been done to the dogs when one adrenal has been removed and as much as 4 erythema doses of x-ray have been given to the other gland. It was noticed that there was more fighting and barking in the pen where the rayed dogs were kept after radiation than in any of the other general pens where larger numbers of dogs were enclosed. This is mentioned to show the condition of the dogs following radiation and is not ascribed to the effect of the x-ray. The dogs which merely had one suprarenal exposed to 4 erythema doses appeared normal in every way for periods of 3, 6, and 9 weeks, respectively.

The dog which had one suprarenal removed and the other one exposed to 5 erythema doses, responded differently. The dog made a rapid and uneventful recovery from both operations of that series. In fact, there was a gain in weight of 3 lbs. during the first 6 weeks following the second operation, above the weight at the time of the first operation. This weight was maintained and the animal appeared in excellent condition for the next 3 months. Approximately 4½ months after radiation there was noticed a very gradual loss of weight reaching about 2.5 lbs. in a month. The condition of the animal seemed good, but the dog did not appear to be as active as previously. The dog looked bright but appeared weak and did not eat the ground meat readily when it was offered. This condition became gradually worse. There was a loss of 5.5 lbs. during the last 3 weeks. One week before death the stools changed from hard, well-formed to soft, mushy stools. A severe diarrhoea soon followed and continued till death. During the last few days the dog showed little inclination to walk about. When given ground meat the dog would lie on his abdomen, eat a little and apparently stop to rest. The exhaustion was very marked.

The chief symptoms were very marked muscular weakness, anorexia and severe diarrhoea. The microscopic examination of the adrenal gland showed extensive destruction of the cells with marked fibrous tissue proliferation about the gland. There were, however, a few cells which appeared normal. The symptoms of this dog resembled very closely the clinical manifestations of Addison's disease. Microscopic examination reveals sufficient destruction to account for the symptoms. We realize that we cannot definitely state that this dog died from adrenal insufficiency, but the findings closely resemble the symptoms as described by Stewart and Rogoff (1925). Also we think it would be inadvisable to draw any definite conclusions based on the findings in one animal, but as we cannot continue this problem we feel that our results should be reported as a suggestive method for the production of Addison's disease. The method which we used seems to be satisfactory for producing a gradual destruction of the suprarenal tissue without apparent injury to any other tissues. Larger doses of x-rays would no doubt hasten the process and should be tried. It is only with the production of the condition experimentally that we can hope to study the therapeutic measures for its alleviation.

The changes in the cholesterol concentration of the blood are opposite to those of the other investigators cited. In three of the four cases in which the right adrenal had been removed, there was a slight decrease in the cholesterol, 21 to 41 days after the operation. After removal of one adrenal and radiation of the remaining gland, there were no significant changes even where there was marked destruction of the cortex. We do not feel that the changes which we observed during the course of these experiments show any relationship between the suprarenals and cholesterol metabolism.

CONCLUSIONS

1. There appears to be no appreciable change in the blood cholesterol following the administration of 3 to 5 erythema doses to the left adrenal after the removal of the right adrenal.

2. The method described is suggested for the production of adrenal insufficiency in dogs.

3. The histological changes in the adrenals following radiation are in proportion to the number of doses administered.

We are indebted to Dr. A. J. Carlson for revision of the manuscript and to Dr. R. H. Jaffee for a study and description of the slides.

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THE ADRENALIN CONTENT OF THE SUPRARENAL CAPSULE IN THE CHICK EMBRYO

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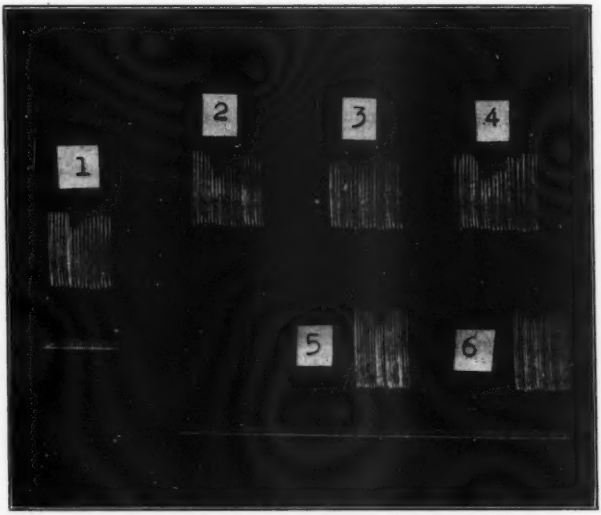
The time of appearance of adrenalin in the suprarenals has often been investigated. Fenger (1912) and McCord (1915) found adrenalin in the sixth week of embryonic life in cows, sheep and pigs. Miller (1926) found adrenalin and the chromic reaction in mice on the 14th and 15th days. Hogben and Crew (1923), using the intestinal assay method, came to the conclusion that adrenalin undoubtedly appears in chicks after the 16th day of embryonic development, but not before the 14th day. Lutz and Case (1925) also studied the chick embryo, using the frog's eye assay method. The presence of adrenalin was always demonstrated after the tenth day; in some, but not all cases it was found as early as the eighth day. As to human embryos, it was observed by Moore and Purinton (1900) and by Thomas (1926) that both adrenalin tests and the chromic reaction failed towards the end of embryonic development.

The present research with chick embryos was undertaken to determine the time when adrenalin appears, the relation between adrenalin and chromic reaction, and the increase of the former with the development of an embryo.

MATERIALS AND METHODS

Eggs of Nagoya-cochin fowls were brought from a neighboring poultry farm one or two days after they were laid. Those of about the same size were selected and laid in an electric incubator of 38° C., and examined in succession at different periods of development. The methods for determining adrenalin are numerous, but each of them has its merits and demerits (Hoskins, 1911; Kodama, 1923). I adopted Cannon's intestinal method (Cannon and de la Paz, 1911). A piece of small intestine is suspended according to the method of Magnus in Ringer's solution (10 to 500 cc.), previously warmed. While the movements are being recorded on the smoked paper of a kymograph the emulsion of suprarenal capsule is flowed into Ringer's solution quietly along the wall of the receptacle. For the emulsion the suprarenal capsules are completely and quickly rubbed in a mortar, and then warm distilled water measuring about one one-hundredth of the

volume of the segment bath is added. The intestinal movement is depressed more or less in all cases. When it is restored to the previous condition, the Ringer's solution is first drawn off, and then the same volume of Ringer's solution of known adrenalin content is added. The same processes are repeated several times. Comparing each, one can easily appreciate the adrenalin content of the emulsion. (See the accompanying figure.)



1: the effect of emulsion of the suprarenal capsules obtained from an embryo of 11th day of incubation. 2, 3, 4, 5, 6: the effect of Ringer's solution containing 0.0006, 0.0002, 0.0007, 0.0005, 0.0004 mgm. of adrenaline, respectively. Time records, 6 seconds.

The points of especial importance in the manipulation are: (1) The temperature should be kept constant; (2) the supply of oxygen also constant and continuous; (3) the emulsion should be made as quickly as possible, and nearly in the same length of time; (4) the last dilution of the fluid should always be the same. From my own experience, the determination is done most favorably when the adrenalin content reaches approximately 0.005 mgm. dl. (5). The addition of emulsion of adrenalin should be conducted most carefully.

The chromic reaction was determined in the following manner: The suprarenal capsule is cut out with the surrounding tissues, fixed about five days in Orth's solution and imbedded in paraffin. The sections are stained with Giemsa or hematoxylin and examined under the microscope.

EXPERIMENTAL RESULTS

1. *The appearance of adrenalin in the suprarenal capsules.* According to von Brunn (1872) and Lillie (1922) the cortex is founded on the fourth or sixth day of incubation and the medulla later than the eighth day. From my own experience it is impossible to separate the suprarenal capsules from other tissues until the sixth day of incubation because of its extreme softness and transparency. Even on the seventh day only scrupulous care leads to success. On and after the eighth day the manipulation grows easier as an embryo develops. With the seventh day embryo the intestinal proof failed in all cases. With the eighth day embryo and those of longer incubation positive results were secured and the increase of the reaction kept pace with the development of the embryo.

2. *The chromic reaction of cells of suprarenal capsules.* The reaction failed before the seventh day of incubation, on which day the medullary cells have not yet entered the cortical substance. On the eighth day one can observe for the first time medullary cells that react with chromic salts. On the ninth day and afterwards the staining as well as the number of cells showed an increment.

3. *The progress of development and the increase in the content of adrenal.* The examination began on the seventh day and continued until the 21st day of incubation. The first day means here the first 24 hours of incubation, and subsequent days each 24 hours, respectively. The 21st day begins at the end of the 20th day and lasts until three hours after the young chick makes itself a tiny hole on the shell with its bill. On and after the 12th day, the glands from each individual were large enough to be used. Before that time, five to ten, or even twenty, glands were rubbed together in a mortar, and the content of adrenalin pro rated. The term "adrenalin content" in the table stands for that extracted from both glands of one embryo. All the results may be summarized briefly in the following tables and curve:

ADRENALIN CONTENT OF SUPRARENALS OF CHICKS

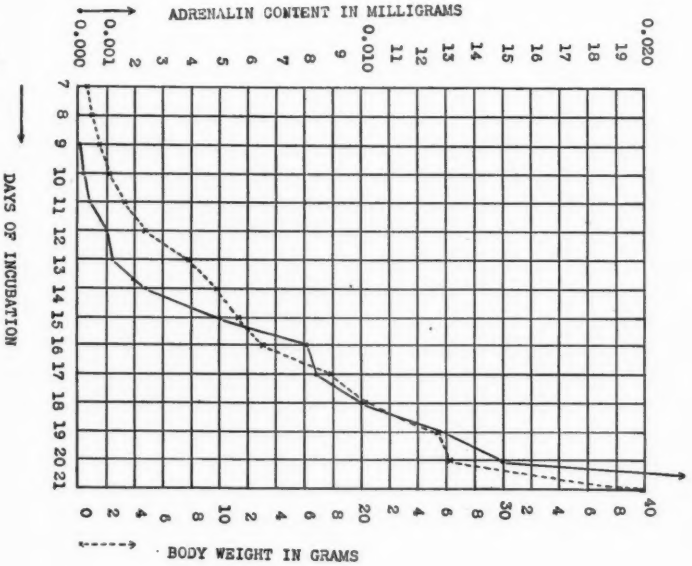
	Average Body Weight Gms.	Adrenaline Content Mgm.	No. of Embryos Used	Volume of Solution Cc.
		The 7th Day of Incubation		
	0.70		10	10
	0.68		20	10
	0.67		20	10
	0.68		20	10
	0.69		20	10
Av.	0.68			
		The 8th Day of Incubation		
	1.01	trace	10	10
	0.91	trace	20	10
	0.98	trace	20	10
	1.02	trace	10	10
	1.01	trace	10	10
Av.	1.00	trace		
		The 9th Day of Incubation		
	1.45	less than 0.0001	10	10
	1.59	0.0001	10	10
	1.50	0.0001	5	10
	1.40	0.0001	5	10
	1.52	0.0001	5	10
Av.	1.51	0.0001		
		The 10th Day of Incubation		
	2.38	0.0002	5	10
	2.23	0.0002	5	10
	2.28	0.0002	5	10
	2.15	0.0002	5	10
	2.25	0.0002	5	10
Av.	2.26	0.0002		
		The 11th Day of Incubation		
	3.26	0.0005	1	20
	3.20	0.0004	1	20
	3.20	0.0005	1	20
	3.00	0.0003	1	20
	3.40	0.0004	1	20
Av.	3.21	0.0004		
		The 12th Day of Incubation		
	4.8	0.0009	1	20
	4.7	0.0009	1	20
	4.8	0.0009	1	20
	5.2	0.0012	1	20
	4.6	0.0010	1	20
Av.	4.8	0.0010		
		The 13th Day of Incubation		
	8.32	0.0013	1	30
	7.00	0.0010	1	30
	8.80	0.0015	1	30
	7.50	0.0012	1	30
	7.05	0.0010	1	30
Av.	7.73	0.0012		

	Average Body Weight Gms.	Adrenaline Content Mgm.	No. of Embryos Used	Volume of Solution Cc.
		The 14th Day of Incubation		
	9.2	0.0028	1	50
	10.3	0.0022	1	50
	9.2	0.0020	1	50
	9.6	0.0020	1	50
	10.5	0.0030	1	50
Av.	9.8	0.0024		
		The 15th Day of Incubation		
	10.75	0.0050	1	100
	11.00	0.0050	1	100
	11.50	0.0050	1	100
	11.40	0.0050	1	100
	12.00	0.0052	1	100
Av.	11.33	0.0050		
		The 16th Day of Incubation		
	14.0	0.0085	1	200
	14.2	0.0085	1	200
	12.5	0.0078	1	200
	12.2	0.0078	1	200
	12.0	0.0070	1	200
Av.	13.0	0.0081		
		The 17th Day of Incubation		
	18.2	0.0082	1	300
	18.4	0.0086	1	300
	17.0	0.0088	1	300
	17.6	0.0081	1	300
	18.1	0.0082	1	300
Av.	17.9	0.0084		
		The 18th Day of Incubation		
	20.2	0.010	1	300
	20.8	0.010	1	300
	21.5	0.011	1	300
	19.4	0.010	1	300
	19.2	0.010	1	300
Av.	20.2	0.010		
		The 19th Day of Incubation		
	25.8	0.013	1	300
	26.1	0.014	1	300
	25.5	0.012	1	300
	25.0	0.012	1	300
	26.0	0.013	1	300
Av.	25.7	0.013		
		The 20th Day of Incubation		
	26.0	0.013	1	400
	26.5	0.017	1	400
	26.4	0.014	1	400
	26.4	0.015	1	400
	26.5	0.016	1	400
Av.	26.3	0.015		
		The 21th Day of Incubation		
	39.6	0.039	1	500
	40.0	0.038	1	500
	39.0	0.039	1	500
	40.7	0.042	1	500
	40.0	0.040	1	500
Av.	39.8	0.039		

Emulsions of heart, liver, spleen, kidney, muscle, etc., were used as controls. Their corresponding quantity was taken at different periods of development and examined under respectively similar conditions. The results proved negative in nearly all cases. Only when they were used in great quantity was the intestinal movement sometimes checked.

SUMMARY AND CONCLUSION

1. In the chick embryo the suprarenal adrenalin appears on about the eighth day of incubation, and chromic reaction of the gland cells sets in at nearly the same time. Their intimate relation, which Ogata (1916) pointed out, is thus confirmed.



2. The adrenalin content of the glands increases gradually with the progress of development in an incubator, but a more or less marked increment is found on the 13th to 14th, and the 20th to 21st days. It is interesting to note that this latter fact and Sendju's work (1925) on tyrosin during the chick's de-

velopment suggest a close relationship between tyrosin and adrenalin.

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Book Reviews

THE ENDOCRINE GLANDS AND AUTONOMIC SYSTEMS IN DEMENTIA PRAECOX. Gabriel Langfeldt, 1926. J. W. Eides Boktrykkeri A/S, Bergen. Pp. 326.

This work represents perhaps the most searching investigation yet reported on the possible endocrine etiology of dementia praecox. The work was done at the Neevingaarden Mental Hospital at Bergen, Norway. Of the 320 patients available, 40 who were unmistakably diagnosticated dementia praecox were selected. These comprised 16 who were clearly catatonic; 11, hebephrenic, and 13 mixed hebephrenic-catatonic.

In each case, in addition to the routine physical examination, careful observations were made on the size of the testes, size of the sella turcica, presence or absence of thymus shadow, condition of epiphyseal lines, blood morphology, basal metabolism, carbohydrate tolerance, presence of clinical signs of vagatonia or sympathicotonia and reactions to adrenalin, atropine, and pilocarpine.

Diffuse thyroid enlargement was found in 13 cases. No definite shrinkage of the testes, as was possibly anticipated, was found, but a marked preponderance in size and firmness in the hebephrenics as contrasted with the catatonics occurred. Lymphocytosis occurred in 7 of the 8 cases of acute catatonia, and in four of the mixed cases that were preponderantly catatonic. In only a single other case was lymphocytosis seen. The basal metabolism was low in 7 of the 8 cases of acute catatonia and in 4 mixed cases (catatonic); it was approximately normal in all but one of the rest of the 40 cases. In a few cases attempts to normalize the basal metabolism with gland products were unavailing. The results as regards glucose tolerance (from blood sugar curves) were not particularly convincing, but seem to show that there is a reduction during the acute phase of the disease. Glycosuria occurred notably more frequently in hebephrenia than in catatonia.

Both clinical and pharmacological findings support rather consistently the conclusion that in the catatonic group there is overactivity of both the sympathetic and parasympathetic nervous systems during the acute and stuporous stages: in the quiescent stage vagatonia alone is found. In hebephrenia, on the

contrary, the evidence points to sympatheticotonia throughout.

The author concludes that the results of this study definitely indicate that endocrine factors play an important role in the etiology of dementia praecox, but precisely what organs are at fault is still questionable. He ascribes a good deal of importance to "status thymicolymphaticus" in catatonia, but in view of the dubious endocrine standing of this "status" the conclusion is not illuminating.

Rather more convincing is the conclusion that the various phases of the manifestations of catatonia are to be explained as a result of a "struggle between the sympathetic and parasympathetic systems." In hebephrenia, on the other hand, the course of the disease is much less eventful because the sympathetic system is dominant throughout.

It cannot be said that Langfeldt has closed the subject—or, indeed, definitely settled any part of it—but he has placed on record a great many careful observations that must be taken into account in any subsequent research on the somatic phase of the dementia praecox problem.

Abstract Department

Blood sedimentation in Addison's disease (La sedimentación globular en la enfermedad de Addison). Bonilla, E. and A. Moya, Med. ibera, **511**: 145-156. 1927.

The authors are making a systematic study of this sedimentation reaction in the endocrinopathies. From their studies in twenty-four cases of Addison's disease they believe that the Fähraeus reaction has diagnostic value. An accelerated sedimentation time appears early in the disease and is a very constant finding. They believe that it has a certain prognostic value in that the graver are the manifestations of the disease the more rapid is the sedimentation.—G. M.

Survival period in the pregnant and lactating cat following adrenal extirpation. Corey, E. L., Proc. Soc. Exper. Biol. & Med. **25**: 167-168. 1927.

The survival period of cats following complete adrenal extirpation was not found to be changed by pregnancy or lactation. These results are in contra-distinction to those reported by other workers for pregnant bitches.—M. O. L.

Correspondence between the subperitoneal nervous plexus and the abdominal paraganglia (Zur Frage über die Wechselbeziehungen zwischen dem subperitonealen Geflecht und dem Paraganglion abdominale). Dowgiallo, N. D., Ztschr. f. Anat. u. Entwcklngsgesch. **83**: 598-604. 1927.

The work is based on a study of 46 dogs, 17 cats and 14 children, and is largely of morphological interest—A. T. R.

Absence of fever in infected rats deprived of adrenal glands (Sur l'absense de fièvre dans l'infection du Rat privé de glandes surrénales). Giaja, J., X. Chahovitch, and A. Giaja. Compt. rend. Acad. d. Sc. **184**: 1680-1681. 1927.

Adrenalectomized rats, infected with a virulent strain of B. pyocyneus, show the same gradual fall of temperature as rats not so infected. Normal infected rats show a distinct rise of temperature of over 2°C. in the same period.—A. T. C.

Adrenalin and muscle tonus (Uber einen peripheren Angriffspunkt der Adrenalinwirkung auf den Muskeltonus). Freudenberg, E. Klin. Wchnschr. **6**: 634-635. 1927.

Following hyperventilation, muscle tetany has been shown to occur in skeletal muscle which has previously been injected with a solution containing novocaine, adrenalin and a potassium salt. Freudenberg reports the following experiment to show the role of adrenalin in the above type of tetany. During a preliminary three-hour period the person on whom the observations were to be made, took 10 g. potassium bicarbonate per os. Into the musculature of one thumb 0.0025 g. adrenalin was injected. Hyperventilation was begun immediately. The spasms which occurred in the injected thumb began sooner, were more intense and lasted longer than those which occurred in the uninjected thumb during and after hyperventilation. The experiment was repeated after 20 minutes with the same results. Identical results were also obtained the next day. The experiment furnishes no criterion as to whether the action is only peripheral or is both peripheral and central.

—M. W. Caskey.

Embryology of the chromaffin system in man (Über die Ontogenese des chromaffinen Systems beim Menschen). Iwanow, G., Ztschr. f. Anat. u. Entwcklngsgesch. **84**: 238-260. 1927.

The study is based on 52 human fetuses from 5 to 290 mm. in length. Largely of morphological interest.—A. T. R.

Topography of the paraganglia in man (Zur Frage der Topographie der Paraganglien beim Menschen). Iwanow, G., Ztschr. f. Anat. u Entwcklngsgesch. **84**: 544-548. 1927.

A schema is given of the locations where paraganglia have been found, extending from the submaxillary gland to the lower portion of the abdominal cavity.—A. T. R.

Hypoglycemia in scleroderma. Longcope, W. T., J. A. M. A. **90**: 1-7. 1928. Abst., A. M. A.

Eight cases of generalized scleroderma have been studied by the author with reference to the function of glands of internal secretion. In one case of generalized scleroderma with deep pigmentation, attacks of mental confusion and delirium occurred repeatedly after short periods of fasting. These attacks were associated with hypoglycemia. The resemblance between many of the symptoms in this case and those occurring in some instances of Addison's disease was noteworthy. In a study of five other cases of generalized scleroderma, the blood sugar, as well as the other chemical constituents of the blood, did not deviate materially from the normal. In three cases the basal metabolic rate tended to fall

below normal and the administration of thyroid extract in these cases was attended by symptomatic improvement. In one fatal instance of acute and extensive scleroderma in a young man, autopsy disclosed atrophy of one suprarenal gland and interstitial orchitis. Longcope suggests the possibility that disturbances in the function of the glands of internal secretion, which occasionally accompany scleroderma, may in some instances occur as a result of involvement of these organs by the generalized process, and thus do not have a direct bearing on the etiology of scleroderma.

Toxic substances of the blood after extirpation of the adrenals (Ueber toxische Substanzen des Blutes nach Exstirpation der Nebennieren). Putschkow, N. M., and A. W. Kibjakow, Arch. f. d. ges. Physiol. **218**: 83-88. 1927.

After adrenalectomy in dogs in certain cases death followed through paralysis of the heart. This was due to accumulation of choline in the blood, following a disturbance of the lipoid transporting function of the liver.—A. T. C.

Studies on cholesterol. III. The relation of the suprarenal gland and the spleen to cholesterol metabolism. Randles, F. S. and A. Knudson, J. Biol. Chem. **76**: 89-93. 1928.

In 17 rats on a cholesterol-free diet removal of the adrenal glands had no effect upon the cholesterol content of the blood. —M. O. L.

Sulfate retention in dogs following bilateral adrenal extirpation. Swingle, W. W., and W. F. Wenner, Proc. Soc. Exper. Biol. & Med. **25**: 169-171. 1927.

Dogs with both adrenal glands removed and presenting marked symptoms of adrenal insufficiency showed a marked increase in the inorganic sulphate of the blood. This increase was most marked when the animal was verging on coma. Inorganic phosphate in the blood was also increased. The author believes that retention of the sulphate and phosphate ions plays a considerable rôle in the acid intoxication of adrenal insufficiency.—M. O. L.

A biometrical study of the size inter-relationship of the glands of internal secretion. Hammett, F. S., J. Metab. Research. **7-8**: 91-163. 1925-1926.

A biometrical study has been made of the weight inter-relations of the glands of internal secretion in a group of 121 males and 121 female albino rats 150 days of age of common inheritance and experience. The various organs show different degrees of association with the body weight and with each other.

Evidence is presented which indicates that in the albino rat up

to the time when the rate of growth becomes that of the mature adult, the physical well-being of the animal is more of a factor in the determination of the onset of thymic involution than is the age or physiological stage of development of the animal as a whole. This brings a new point of view to bear on the conception of this phenomenon. The only specific association exhibited by the thyroid is with the adrenals. This occurs in both sexes and is positive in direction. It supports the idea of a special functional inter-relationship between these two organs. The association is greater in the male than in the female. The adrenals are positively and specifically correlated with all of the other endocrine glands save the hypophysis in both sexes. The adrenal-pancreas association in the male is only a possibility. Analysis shows that the adrenals can be considered as a weak integrating mechanism binding together certain of the other incretory organs into an associative relationship. This influence is apparently more far-reaching in the female than in the male, and is attributable to the greater degree of association between adrenal weight and gonad weight in the former sex. It may mean that the adrenals are more important factors in the bodily economy of the female than they are in that of the male. The gonads show no particular predilection for specific weight correlation with any of the incretory organs save the adrenals. A weak positive correlation exists between ovary weight and hypophysis weight in the female, and a tendency toward weak negative ovary-thyroid and testis-thymus correlation seems to be present. The hypophysis is similarly unresponsive to weight changes in the other endocrine glands. In the female the gland shows only a weak positive correlation with the gonads. In the male a weak positive association with the pancreas is in evidence, and a possible weak negative correlation with the thymus. This situation is taken to indicate that the hypophysis either plays little special part in the activities of the other organs of internal secretion, or that it is largely uninfluenced by their variations. In the female the only specific association exhibited by the thymus is with the adrenals. This is positive in direction. In the male, on the other hand, a general, though weak tendency for weight association is present. This is definite, specific and positive with the pancreas and the adrenals. As with the thymus so with the pancreas, in the female the only specific association is with the adrenals, and this is only weakly positive. In the male, on the other hand, definitely specific though weak correlations are exhibited between the pancreas weight and the weight of the hypophysis and the thymus. There is the probability of a pancreas-adrenal association. These findings are not consistent with the idea that the glands of internal secretion are to be considered as a systemically specific functionally inter-related group in the normal organism. The organ of greatest variability in both sexes is the thyroid. The thymus is next in line. The adrenals,

gonads, hypophysis and pancreas fall into a group of definitely lower variability, which indicates a lesser sensitivity to the variability producing factors aside from those carried by the body weight and the other incretory organs.—Author's Abst.

Cyclic changes in the ovary of the mole (Untersuchungen über das Ovarium von Talpa europaea mit besonderer Berücksichtigung seiner cyclischen Veränderungen). Altmann, F., Ztschr. f. Anat. u. Entwcklngsgesch. **82:** 482-569. 1927.

Serial sections of the ovaries of 98 specimens, representing every month of the year, were analysed by projecting them upon paper at various magnifications and then weighing the paper representing the various constituents. Of these animals, 31, were killed in March during the active sexual period and pregnancy. The interstitial cells decrease greatly during the active sexual period in the spring. This and the other elements in the ovary are discussed from the standpoint of their probable function.—A. T. R.

Significance of pseudoepiphyses in endocrinology (Über die Pseudoepiphysen und deren Bedeutung in der Endocrinologie). Rochlin, D. G., Ztschr. f. Anat. u. Entwcklngsgesch. **82:** 354-367. 1927.

As a rule there is no epiphyseal ossification center on the distal end of the phalanges, first metacarpal and first metatarsal bones and on the proximal end of the second, third, fourth and fifth metacarpal and metatarsal bones. A more or less independent ossification center in any of above locations gives origin to what is termed a pseudoepiphysis. Pseudoepiphyses are most frequent in infantile retarded development and apparently where the endocrine disturbance is pluriglandular. Hypothyroidism seems to play a large role. Usually there is also hypogenitalism, but the sex glands are not considered to be a cause of the pseudoepiphyses. A pseudoepiphysis is especially frequent on the middle phalanx of the fifth finger. Bones with a pseudoepiphysis are usually too short. Pseudoepiphyses were not encountered in cases of excessive growth of bones in length nor in cases of accelerated differentiation, e.g., as in Basedow's disease and pubertas praecox. The report is based on 40 original cases with pseudoepiphysis, 32 of which were especially selected. The anomaly was present in 5.2 per cent of children from 2 months to 10 years of age.—A. T. R.

Uterine and mammary development following injection of the ovarian hormone (Développement utérin et mammaire par injection d'hormone ovarienne). Champy, C., and T. Keller, Compt. rend. Acad. d. Sci. **185:** 302-304. 1927.

Continuous injections into castrated female guinea-pigs produce in 5 days phenomena comparable to those of the oestral pe-

riod, and in from 10 to 25 days uterine development comparable with that in pregnancy, with formation of decidual cells, a secondary mucous transformation of the vagina, and hypersecretion of its glands. Such injections into male guinea-pigs, whether castrated or not, produce similar marked development of the mammary glands to those produced in females, the maximum effects being produced in 15 to 18 days.—A. T. C.

The variation in the unit of the oestrus-producing hormone. Coward, Katherine H., and J. H. Burn, J. Physiol. **63:** 270-279. 1927.

An effort was made to obtain a more refined standardization of the hormone since it was found that a variation of 700% was sometimes found in the size of the dose of a given lot of the extract necessary to produce oestrus in ovariectomized rats. There was no correlation between body weight and the dose necessary to produce oestrus. Regeneration of ovarian tissue was found to have occurred in only 2% of rats and in 7% of mice. No significant differences were found between intraperitoneal and subcutaneous injections. Forty per cent of individual rats showed great irregularity in response to successive doses of the same size. The rat unit is "redefined as that amount of extract which produces oestrus in 50% of ovariectomized rats." The dosage for the mouse unit is the same as for the rat, although the latter averages 7.5 times the body weight of the former, so concentration in body fluids is not an important factor.—C. I. R.

The effects of hysterectomy on the system of sex organs and on the periodicity of the sexual cycle in the guinea pig. Loeb, L., Am. J. Physiol. **83:** 202-224. 1927.

Hysterectomy in the guinea pig, by prolonging the life and functional activity of the corpus luteum, interferes with the typical cyclic activity of the ovary and other reproductive organs and brings about the essential changes characteristic of pregnancy. These effects vary quantitatively according to the amount of uterus removed. How the operation causes these results is not clear. The similarity in the effects of hysterectomy and pregnancy on the corpus luteum suggests the possibility that a functional inactivity of the mucosa of the pregnant uterus is responsible for the prolonged functional activity of the corpus luteum.—E. P. Durrant.

On ovarian hormones (Prüfung des Hormongehaltes von Corpus luteum präparation. XI. Über weibliche Sexualhormone). Loewe, S. and F. Lange, Arch. f. exper. Path. u. Pharmakol. **120:** 48-64. 1927. Abst., Physiol. Absts. **12:** 519.

The effect of ovarian preparations on the cycle of changes in vaginal smears of normal mice was studied. No activity was detected in agomensin, sistomensin, or luteoglandol.

Creatinuria and castration. Shen, T. C., Chinese J. Physiol. **1**: 363-366. 1927.

The urinary creatine in dogs and albino rats was followed before and after castration. No demonstrable relationship was found between the male genital glands and creatine metabolism.—L. G. Kilborne.

The Steinach operation (Die Ergebnisse der Steinach-Operationen). Stettiner, H., Deutsche med. Wchnschr. **44**: 1861-1863. 1927.

A review is given of German literature on the Steinach operation. The author contents himself with giving opinions of various authors without attempting to evaluate them or to arrive at any conclusion.—R. M. Oslund.

Oestrus periods of rats in parabiosis (Über das Verhalten der Brunst bei der Parabiose der Ratten). Zacherl, H., Klin. Wchnschr. **6**: 1614-1615. 1927.

In nonpregnant rats joined together by colioanastomosis the authors observed that when the periods of heat did not fall together before the union, they never became synchronized afterward. The oestrual cycles continued to be completely independent of one another. Pregnancy of the one did not prevent oestrual cycles in the nonpregnant partner. When the parabiotic pair consisted of a male and a female, oestrus disappeared a few days after the union was made and did not return so long as they were united. Similarly when the junction was made between a female with normal oestrual cycles and a castrated male or female there was cessation of oestrual cycles.—C. P. Stone.

A hormone of heart beat. VIII. Radiation experiments with fluorescent, ultraviolet, and Röntgen rays (Ueber ein Hormon der Herzbewegung. VIII. Bestrahlungsversuche mit Fluorescenz—Ultraviolett—und Röntgenlicht). Haberlandt, L., Arch. f. d. ges. Physiol. **218**: 129-136. 1927.

The active compound obtained in Ringer's solution from the frog's heart is partly but not completely decomposed by strong fluorescent and ultraviolet light. Aqueous extracts are largely decomposed by strong Röntgen radiation.—A. T. C.

Influence of diuretics on pituitrin secretion (Untersuchungen über die Beeinflussung der Pituitrinsekretion durch Diuretica). Hoff, H., and P. Wermer, Klin. Wchnschr. **6**: 1180-1181. 1927. Abst., Physiol. Absts. **12**: 512.

Diuresis was produced in dogs with euphyllin, novasurol, or urea, and cerebro-spinal fluid was withdrawn at intervals (from the cysterna magna) and tested for pituitary secretion by the virgin

guinea-pig uterus. Much more was present than before the diuresis. An opportunity to carry out the same test on a patient who underwent suboccipital puncture for diagnostic purposes showed also that, after euphyllin, there was an increased amount of pituitary secretion in the cerebro-spinal fluid. In three cases of idiopathic diabetes insipidus pituitrin was recognized in the suboccipital puncture fluid. The amount was not increased by euphyllin injection. It is concluded that diuresis stimulates the pituitary gland to secrete. Morphia and ether narcosis prevent this action, but chloretone does not affect it.

The active principles of the posterior lobe of the pituitary gland. I. The demonstration of the presence of two active principles. II. The separation of the two principles and their concentration in the form of potent solid preparations. Kramm, O., T. B. Aldrich, I. W. Grote, L. W. Rowe and E. P. Bugbee, J. Am. Chem. Soc. **50**: 573. 1928.

The posterior lobe of the pituitary gland contains two important active principles: one which raises blood pressure and another which stimulates contraction of uterine muscle. A substantially complete separation of these two active principles has been accomplished by the employment of salting-out methods and, subsequently, by the use of appropriate solvents and precipitants. Solutions of these separated active principles have been recombined to form a pituitary extract identical with the original from which they were prepared, thus proving that no decomposition has taken place. The substantially pure pressor principle (beta-hypophamine) has been obtained in the form of a white, stable, water-soluble powder 80 times as potent as the International Standard Powdered Pituitary. The separated oxytocic principle (alpha-hypophamine) has been obtained in the form of a white, stable, water-soluble powder which is more than 150 times as potent as the International Standard Powdered Pituitary. The pressor principle has been shown to be responsible for the diuretic-antidiuretic action of pituitary extracts. The pressor principle when tested on animals for demonstration of pressor effects shows the development of tolerance which is characteristic of active pituitary extracts. It has been shown to possess no appreciable depressor action. Both active principles are basic bodies, presumably amines. Practical manufacturing methods have been developed for the separation of these two hormones and they have been made available to the medical profession for careful clinical trial. As a result of this preliminary work the foundation is now laid for an investigation of the chemical nature of the separated hormones of the posterior lobe of the pituitary gland, together with a more exhaustive study of their pharmacological properties.—Authors' Abst.

Hypophysin and glycogenesis (Hypophysine et glyconéogénèse). Nitzescu, I. I., and Marie Benetato, Comp. rend, Soc. de Biol. **98:** 58-60. 1928.

In rabbits, injection of posterior lobe extract causes an increase in glycogenesis in the liver and reduction, i. e. mobilization of muscle glycogen. This is true in both starving and well fed animals. —J. C. D.

Changes in the hypophysis of the rat during pregnancy (Über die Veränderungen der Rattenhypophyse in der Gravidität). Schenk, F., Ztschr. f. Konstit. **12:** 703-711. 1926.

Twenty-five pregnant and numerous male and non-pregnant rats were investigated histologically. Pregnancy changes in the hypophysis of the rat are not as striking as in the human. The eosinophilic cells of the anterior lobe of pregnant rats stain less intensely and are less granular than in non-pregnant. The nuclei of these cells become less regular and the whole cell decreases in size. Other changes in the cytoplasm and nucleus indicate that many eosinophilic cells degenerate. Some of the chromophobes, or chief cells, seems to increase. Thus the sections stain with much less contrast. Six to eight weeks after littering some of these changes may still persist.—A. T. R.

Dyspituitarism of the Lorain type, associated with a pituitary cyst arising from Rathke's cleft and secondary lesions in the hypothalamic region and ventricles. Worster-Drought, C., W. C. C. Dickson, and B. W. C. Archer, Brain, **50:** 704-718. 1927.

The condition described was present in a girl of 19, whose general appearance suggested a slender child of 6 or 7 (height 49 inches, weight 47 lbs.). No secondary sex characters had developed. The mental age was 13, and intelligence quotient 0.7. She died shortly after admission to hospital, death probably being caused or hastened by rupture of the cyst. The autopsy revealed the condition indicated in the title. If the pituitary possessed any function it could be but slight, since only remnants of both posterior and anterior lobes were present, as also of the hypothalamic region of the brain. This perhaps suggests that the Lorain type is apituitarism in contrast with dyspituitarism in the Fröhlich type. —A. T. C.

The liver as the organ of sanguinification. Adamson, J. D., Canad. M. Ass. J. **18:** 147-150. 1928.

Equally good and parallel results were obtained in two cases of pernicious anemia placed on liver diet, and two to whom Collip's extract of liver was administered.—A. T. C.

Changes in the eyeground in vascular diseases and in related conditions. Altnow, H. O., Arch. Int. Med. **40**: 757-785. 1927.

A study of twenty cases of thyroid disease with increased basal metabolism shows a rather striking absence of retinal arteriosclerosis when patients in the sixth decade are eliminated. In forty-seven diabetic patients of all ages (excluding children under 12 years) with and without hypertension, the incidence of definite retinal arteriosclerosis was 36.1 per cent in the latter and 81.8 per cent in the former. In both groups considered together, it was 42.5 per cent. These observations indicate that hypertension may play an important role in diabetes. The average age of diabetic patients with definite retinal arteriosclerosis was 57.7 years, while in patients showing doubtful or no retinal arteriosclerosis, the average age was 33 years. No patient under 30 years of age showed either definite or doubtful arteriosclerosis. If the presence of retinal arteriosclerosis is an index of sclerosis of the small vessels in other parts of the body (pancreas included), sclerosis of the small vessels may be an important factor in the production of diabetes after 50 years of age. Likewise, it does not appear to be a factor in the production of diabetes in the young person. Sclerosis of the choroidal vessels is more frequent in diabetes than in the other conditions studied. Changes in the disk are infrequent. If the ophthalmologist or internist sees eyegrounds exhibiting abnormally red retinas, numerous small round hemorrhages, groups of small yellowish-white and grayish-white spots on the central field of the retina, arteries with sclerotic changes, and well defined sclerosis of the choroidal vessel in the periphery of the retinal field with normal or nearly normal disks, in a person past middle life, he should strongly suspect diabetes.—From Author's Abst.

Insulin and carbohydrate tolerance. Brace, W. M., Ann. Int. Med. **1**: 203-211. 1927.

Five selected cases of diabetes were placed on Newburgh and Marsh diets with just enough insulin to keep the urine sugar free. These patients received insulin daily for long periods of time, (32-45 months). From his results the author concludes that insulin is not capable of effecting a cure or a partial cure of human diabetes mellitus because the glucose tolerance was not increased.—E. L.

Effect of glucose on the ketone body excretion in fasting depancreatised dogs. Chaikoff, I. L. and J. J. Weber, Proc. Soc. Exper. Biol. & Med. **25**: 212-213. 1927.

In completely depancreatized dogs, glucose administration was found to have no antiketogenic action.—M. O. L.

The conservative treatment of gangrene complicating diabetes. Harbinson, J. E., Ann. Int. Med. **1**: 212-226. 1927.

A good review and discussion of the medical treatment of diabetic gangrene. An excellent bibliography is appended—E. L.

Quantative and optimal action of insulin (Über die quantative and optimale Wirkung des Insulins). Holm, K., Arch. f. exper. Path u. Pharmakol. **121**: 368-386. 1927.

It was previously shown that when the total subcutaneous dose of insulin was divided and injected at intervals the hypoglycemia appeared just as quickly but was stronger and more lasting than when the insulin was injected in one dose. The same observation was made with the continuous intravenous injection of insulin. The experiments in this paper deal with attempts to find the amounts of insulin required by a dog before and after depancreatization and with and without the administration of glucose. The insulin was given by the continuous intravenous method. The experiments were continued four weeks after extirpation. The weight of the animal decreased from 9.3 to 6.3 kgm. It was found that the normal dog maintains a normal blood sugar at an injection rate of 0.25 unit per hour. After depancreatization the insulin requirement is at first the same but gradually shrinks until not more than 0.065 unit per hour can be given without lowering the blood sugar. The author thinks that in a glycogen-rich animal the excess insulin may be "buffered" by the glycogen; there may also be an opposing action of adrenalin. The alimentary hyperglycemia produced in the dog, when sufficient insulin is continuously given to maintain a normal sugar level without food, differs from that in the intact animal. The fall in the curve is much slower and there is no subsequent hypoglycemia. This is because there is no endogenous source of insulin. Insulin and adrenalin secretions appear to be influenced in opposite directions by the amount of the blood sugar. If one covers the resting metabolism completely by the intravenous injection of glucose (in this case 3.5 grams per hour) then the insulin requirement is six times as great as in the fasting state, that is 0.4 unit per hour. The carbohydrate equivalent of insulin according to this experiment is 8.75 grams glucose per unit. A man weighing 60 kgm. would, therefore, require 7.8 units per day if he were fasting and without a pancreas, while he would require 48 units if his resting metabolism were covered by sugar. The author concludes that most of the experiments described in the literature dealing with the physiological effects of insulin really deal with its toxic action.—N. R. Blatherwick.

Contributions on the action of insulin. II. Insulin-Adrenalin antagonism (Beiträge zur Wirkung des Insulins. II. Mitteilung: Insulin-Adrenalin-Antagonismus). Issekutz, B. v., Biochem. Ztschr. **183**: 283-297. 1927.

A perfusion apparatus for use with the livers of rabbits is described in detail. The author was able to determine simultaneously the rate of formation of sugar, acid and CO_2. The effects of adrenalin were an increase in the formation rate of sugar (if pH is below 7.5), and an increase in the formation rate of acid. The effect of insulin was a decrease in the rate of acid formation. A decrease in the rate of sugar formation could not be demonstrated, nor could a synthesis of glycogen. The decreased acid formation rate with insulin was explained tentatively on a basis of more rapid oxidation of the formed acids. In the presence of insulin, adrenalin failed to accelerate the rate of formation of either acid or sugar.
—B. S. Walker.

Influence of nickel and of cobalt on the hypoglucaemic action of insulin in the rabbit (Influence du nickel et du cobalt sur l'action hypoglycémiante de l'insuline chez le lapin). Labbé, M., H. Roubeau, and F. Nepreux, Compt. rend. Acad. d. Sc. **185**: 1532-1534. 1928.

Nickel and cobalt salts augment and prolong insulin hypoglucaemia.—A. T. C.

Action of nickel and cobalt salts on the hypoglucaemic power of insulin on the diabetic (Action des sels de nickel et de cobalt sur le pouvoir hypoglycémiant de l'insuline chez le diabétique). Labbé, M., H. Roubeau, and F. Nepveux, Compt. rend. Acad. d Sc. **186**, 181-183. 1928.

Is observable in diabetic patients.—A. T. C.

Case of insulin edema. Leifer, A., J. A. M. A. **90**: 610-611. 1928; Abst., A. M. A.

Leifer relates the case of a man who had diabetes and who developed a severe edema following the administration of insulin. Twenty-five units of insulin was given the first day. The next day, June 16, the patient already felt much better, and was given 30 units of insulin. June 17, 18, 19 and 20, he received 30 units of insulin daily but continued to have four plus dextrose in the urine and high blood dextrose, although he felt much better. His weight had already climbed to 141 pounds (64 Kg.). He was receiving a diet containing 750 calories at this time. No edema was visible. The carbohydrate in the diet was increased in greater proportion than was the protein or fat. June 21, 22 and 23, the patient received 50 units of insulin daily; on the 22d, pitting edema of the legs was first observed. The patient felt so well now that he insisted on going back to work but was not permitted to do so. The urine for the first time on the 24th contained no acetone, diacetic or betaoxybutyric acids, and only a trace of dextrose. On the 25th. his weight was 151 pounds (68.5 Kg.) and there was definite edema

of the lower extremities. The fluid intake was very slightly reduced but the salt intake was markedly reduced. Within ten days his weight came down to 139 pounds (63 Kg.) although his diet was gradually increased, and 40 units of insulin was being given daily He has remained sugar free, feeling well and weighing between 137 and 140 pounds (62 and 63.5 Kg.). The edema is gone.

The induced blood sugar curve found in muscular atrophy (La curva de glucemia provocada en la atrofia muscular). Marañon, G., Boll. d. Soc. Española de Biologia, **2**: 43-59. 1926.

Marañon has made an investigation in five cases of muscular atrophy, determining the hyperglycemic curve by means of the determination of fasting glycemia at intervals of the half hour and hour following the injection of 25 grams of glucose in 200 cc. of water. He found the gradual curve of pre-diabetes in four cases. From these observations he concludes that the progressive muscular atrophy probably causes an unbalance of carbohydrate metabolism in the sensitive pre-diabetic. This alteration is regarded as due to depression of glucose consumption by the atrophic muscle. The other factors regulating carbohydrate metabolism doubtless compensate this muscular factor rapidly, hence glycosuria appears only in the pre-diabetic state. The intensity of the hyperglycemic reaction is correlated with the degree of muscular atrophy.—E. B.

Acid base equilibrium in Addison's disease (El equilibrio acido básico en la enfermedad de Addison). Marañon, G., and M. Sarda, Siglo méd. **80**: 197-199. 1927.

The acid base equilibrium has not hitherto been studied in Addison's disease. In six cases the authors found four in which there was a manifest decrease in the alkaline reserve and in the two others a tendency to this condition. There appeared to be a definite relationship between the degree of alkaline depletion and the intensity of the general picture. The authors surmise that the comatose termination of Addison's disease may be due to acidosis. The observations suggest the desirability of alkaline therapy in Addison's disease, especially in the advanced forms when acidosis is manifest. Insulin, which is too often used in different forms of acidosis should not be employed in Addison's disease on account of the marked susceptibility to this hormone unless large quantities of glucose are previously given.—E. B.

A case of chronic glycosuria, probably of extra-pancreatic etiology. Mason, E. H., and R. A. Flack, Canad. M. A. J. **17**: 1294-1299. 1927.

A woman, following pregnancy in 1916, exhibited almost constant slight glycosuria but without symptoms of diabetes mellitus,

and with a renal threshold of 0.07% glucose and normal fasting blood sugar. After administration of 100 grams glucose by mouth blood sugar rose to 0.185% and there was appreciable delay in its decline. During following years there was no restriction in diet. Eight tests made during a second pregnancy in 1921-2 showed glycosuria on only one occasion. Subsequently glycosuria has been constant. Re-examination in 1927 showed fasting blood sugar over 0.15%. After two days on low carbohydrate diet it fell to 0.10%. Renal threshold for glucose was now 0.14% and after 100 grams glucose by mouth blood glucose rose to 0.37% in two hours and fell slowly. Respiratory studies indicated that there was present no marked impairment of glycogen storage, nor of glucose oxidation, suggesting that this case does not accord with the fundamental conception of true diabetes mellitus. The authors suggest that there is present a hyperactive sympathetic nerve supply to the liver, maintaining an excessive rate of glycogenolysis of liver glycogen, independent of any pancreatic disturbance.—A. T. C.

Diabetes among the Chinese: Danger of insulin usage. Mills, C. A., China M. J. **41**: 914-921. 1927.

The author points out that insulin should be used with particular caution in Chinese since they appear to be hypersensitive to it. Of 22 Chinese diabetics treated with insulin three died in insulin shock, one died two days after a severe insulin reaction and two others had severe reactions from which they recovered. The hypoglycemic reactions, when they occurred, were very severe and protracted, and a large amount of glucose was required to secure recovery. As a rule, however, diabetes among the Chinese tends to be mild in type, and in most instances is accompanied in its onset by acute purulent infections. Calculated on the basis of hospital statistics diabetes is almost four times as frequent among Chinese males as among females.—L. G. Kilborne.

Rapidity of sedimentation of red blood cells in human diabetes (Vitesse de sédimentation des globules rouges dans le diabete humain). Nitzescu, I. I., and J. Gavrila, Compt. rend. Soc. de Biol. **98**: 63-64. 1928.

The red cells, as tested by the authors' method, settle more rapidly in diabetics (32 cases) than in normal humans. The more severe the condition, the more rapid the settling. This is but slightly modified by insulin treatment and is not dependent on the amount of blood cholesterol.—J. C. D.

The injection of insulin and thyroid in large doses in the cachexia of nurslings (Las inyeciones de insulina y de extracto tiroideo a altas dosis en las caquexias de los lactantes). Nobecourt and Levy, Progresos de la clínica, **179**: 523-535. 1926.

The authors recommend the treatment of these cachexia states by the injection of insulin (3, 4 or 5 units per kgm. body weight) daily in single or divided doses immediately before giving the sweetened beverage. The injection is preceded by 10 to 40 cc. of glucose serum in order to prevent possible accidents. The treatment is carried on 10-15 days and can be repeated if necessary. The injection of liquid thyroid extract is also useful in the cachexia states. This may be employed in concentration of 10 centigrams per cc. administered in doses varying from 0.25 to 0.1 grams. The increase of weight obtained by this treatment is believed to be due to fixation of water by the tissues, but a possible trophic action of these products is not excluded.—E. B.

Insulin and the mortality rate from diabetes mellitus. Rabinowitch, I. M., Canad. M. J. **17**: 1415-1424. 1927.

Rabinowitch has made a careful statistical study of the data available from the diabetic clinic of the Montreal General Hospital from 1921 to 1927 inclusive. The results show definitely that the use of insulin has produced a lowering of the mortality rates. During the same period diabetes mortality statistics for many large cities and districts in America and Europe do not show a decrease, and some show an increase. The cause of this apparent discrepancy is discussed, and it is considered due to insufficient diet-insulin control.—A. T.

Lowering of blood sugar through parasympathetic stimulation (Experimentelle Beiträge zur Wirkung der Parasympathikusgifte auf den Blutsucker. IV. Fortsetzung der Untersuchungen über Herabsetzung des Blutsuckers durch Parasympathikesreizung). Sakurai, T., J. Biochem. **8**: 365-370. 1928.

By the use of selective parasympathetic stimulants, ergotoxin and pilocarpine, the blood sugar of rabbits was lowered.—M. O. L.

The effect of glucose on ketosis. Selle, W. A., Proc. Soc. Exper. Biol. & Med. **25**: 219-221. 1927.

In four completely depancreatized dogs the administration of glucose by mouth or hypodermically, failed to diminish the ketone bodies of the urine. In two cases an increase was observed in the acetoacetic acid during the experiment. In one case, hydroxybutyric acid also was increased.—M. O. L.

The hypoglucaemic properties of galegine sulphate (Sur les propriétés hypoglycémiantes du sulfate de galégine). Simonnet, H. and G. Tanret, Compt. rend. Acad, d. Sc. **185**: 1616-1617. 1927.

In the normal dog and man administration of galegine sulphate may produce a fall of sugar exceeding 20%.—A. T. C.

The glycemic curve in states of prediabetes (Las curvas de glucemia en los estados prediabeticos). Soler, B., Ann. Acad. Medico Quirurgica Española, **6**: 382-393. 1927.

Utilizing Marañon's technic, Soler studied the glycemic curve in various dermatoses (psoriasis, erythema, syphilis, varicose ulcers, recurrent erysipelas, ferunculosis, etc.). He frequently found the pre-diabetic curve. He regards the recognition of this state as important in its relation to treatment.—E. B.

Is insulin inactivated by glucose? du Vigneaud, V., J. Biol. Chem. **73**: 275-283. 1927.

Twenty-two separate experiments were run in the attempt to demonstrate an inactivation of insulin by glucose, using on an average five rabbits for each experiment. The decrease in blood sugar obtained in the test animal was often slightly less than that in the control. The difference, however, was not great enough to be interpreted as indicating definitely an inactivation, in view of the great variability in the response of rabbits to insulin. In certain experiments where it appeared that inactivation had resulted, the use of more rabbits negatived the difference between control and test. The average decrease in blood sugar of 60 tests was 41.8 mgm. per 100 cc. of blood; the average of 44 controls as 45.1.

—Author's Abst.

The sulfur of insulin. du Vigneaud, V., J. Biol. Chem. **75**: 393-405. 1927.

If the active principle itself actually contains sulfur, as there is good reason to hold, then it is believed that the evidence presented in this study indicates that this sulfur is present as the disulfide linkage and that insulin is most likely a derivative of cystine. By means of the phosphotungstic reaction it was found that as the insulin became more purified the cystine content increased. The proportionality was so striking that it has given hope that this might prove to be a suitable means of assay for purified preparations. When the sulfur was split out, the disulfide linkage was destroyed and the test for cystine greatly reduced in intensity, indicating this as the source of the labile sulfur. Since it has been shown that insulin itself does not give the specific Sullivan reaction for cystine, and since the presence of cystine in the hydrolyzed insulin preparations has been demonstrated, it must be concluded that the cystine is present as some derivative. The behavior of the sulfur in insulin is quite parallel to the behavior of the sulfur in amino acid derivatives of cystine and suggests that the cystine in insulin is linked to the rest of the molecule by a peptide linkage. In this connection the high arginine, histidine, and tyrosine contents of purified preparations might be recalled. In Abel's analy-

ses the calculated empirical formula of $C_{45}H_{75}O_{17}N_{11}S$ is based upon the presence of 1 sulfur atom in the molecule. From this work on the presence of the disulfide linkage the minimum value would have to be twice that given, or $C_{90}H_{150}O_{34}N_{22}S_2$.—Author's Abst.

Cause of increase of insulin in the blood of pancreatic vein following intravenous injection of synthaline (Sur les causes de l'augmentation de la teneur en insuline du sang veineux pancréatique après l'injection intraveineuse de décaméthylènediguanidine). Zunz, E., and J. LaBarre, Compt. rend. Soc. de Biol. **97**: 1801-1802. 1927.

As shown by studies on dogs, this condition depends on stimul received through the vagi.—J. C. D.

The effect of hypercalcemia on the creatin output in myasthenia gravis. Berglund, H., Grace Medes and Anne Lohmann, Proc. Soc. Exper. Biol. & Med. **25**: 204-205. 1927.

In a patient with myasthenia gravis and creatinuria, fed on a creatine-free diet, the blood calcium was caused to rise from 10.6 to 13.3 mgm. per 100 cc. by the administration of parathyroid hormone and calcium lactate. No changes were found in the excretion of creatine.—M. O. L.

Do blood and serum contain some protective agency against the sequelae of parathyroidectomy? (Enthalten Blut und Serum einen Schutzstoff gegen die Folgen der Parathyroidektomie?) Greenwald, I., Arch. f. d. ges. Physiol. **218**: 169-175. 1927.

Theoretical and experimental evidence is adduced against this view.—A. T. C.

The standardization of parathyroid activity. Hanson, A.M., J. Am. M. Ass. **90**: 747-748. 1928.

Use is made of the fact that relatively small doses of the parathyroid hormone will restore parathyreoprivic dogs to normal. The reaction is more uniform than the hypercalcemia of normal animals. Parathyroid extract, for clinical use, should be standardized against a known hypocalcemia. The use of a smaller, accurately standardized unit avoids the danger of inducing a marked hypercalcemia.
—R. G. H.

Treatment of tetany and spasmophilia in adults by bone transplantation. Krinizki, J. M., Arch. f. klin. Chir. **147**: 530. 1927. Abst. J. A. M. A. **90**: 66.

In a previous communication the author showed that a state of hypercalcemia can be produced in a guinea-pig by means of bone

transplantation. The experiment was later applied to human beings afflicted with surgical conditions associated with spasmophilia or tetany. This resulted in a rapid disappearance of spasmophilic symptoms and an associated rise in the blood calcium level. Heterogenous transplants proved to be just as efficient as homogenous. Ordinary soup bone may be used. He transplanted a piece of bone measuring about 5 cm. by 3.4 cm. by 0.5 cm. into the subcutaneous tissues. In his opinion, the result obtained cannot be explained on the basis of the transplant acting as a depot of calcium. One is lead to believe that some hitherto unexplained reciprocal action between the transplant, the parathyroid hormone, the blood and the tissues takes place.

The use of parathormone in the treatment of infantile tetany. Leitch, D. B., Canad. M. A. J. **17**: 1321-1323. 1927.

In a series of seven cases of infantile tetany parathormone (Lilly) was injected subcutaneously, 40 units a day, without any other medication. There followed rapid disappearance of symptoms of tetany, accompanied by increase of blood calcium, indicating that the internal secretion is in itself effective, though it is considered that the usual treatment should include in addition administration of calcium lactate and cod liver oil.—A. T. C.

The effect of CO_2 administration upon parathyroid tetany. Swingle, W. W., W. F. Wenner and P. Stanley, Proc. Soc. Exper. Biol. & Med. **25**: 165-167. 1927.

In dogs suffering from tetany experimentally induced by parathyroidectomy, the symptoms were markedly relieved by CO_2 administration. This relief lasted for several hours, and the effect could be repeated. The serum calcium level was not changed but the blood lactic acid was increased from about 27.5 mgm. to 100 mgm. per 100 cc. following CO_2 treatment.—M. O. L.

Pineal pathology. Horrax, G. and P. Bailey, Arch. Neurol. & Psychiat. **19**: 394-414. 1928.

Horrax and Bailey present three case studies as evidence on the pineal problem. The first, that of a boy of 9, showed slight pubertas praecox, with spermatozoa formation and a large pinealoma. Whether the tumor was productive or destructive is not clear. In a second case a man of forty was found to have normal mental and physical development with the pineal entirely replaced by a ganglioneuroma. The third patient was sexually mature at the age of three. He had a large tumor of the third ventricle but a normal pineal body. The thyroid, adrenals and hypophysis were also normal, according to autopsy study.—R. G. H.

The clinical and experimental studies on the effect of quinin upon the nitrogen metabolism of hyperthyroidism. Aoki, K., Folia Endocrinol. Japonica, 3: 47-49. 1928.

In three dogs the feeding of desiccated thyroid gland substance caused an increase in total nitrogen, ammonia and creatin-nitrogen. Urea nitrogen was decreased and the ratio of creatinin to total nitrogen was not changed. When quinin muriate was administered with thyroid gland substance the changes in the nitrogen partitions were less marked.—M. O. L.

The thyroid in infections and toxemias. Cole, W. H., and N. A. Womack, Proc. Soc. Exper. Biol. & Med. 25: 188-191. 1927.

In 7 dogs which succumbed to peritonitis, pneumonia and such severe infections, the iodine content of the thyroid was compared to that of 7 control dogs of equal weight which were kept and fed under the same circumstances as the dogs which died from infection. Analyses revealed 0.147 mgm. iodine per kgm. of body weight in the thyroids of the dogs with infection and 0.382 mgm. per kgm. body weight in the thyroids of the healthy control dogs. The weights of the thyroids, however, varied in a reverse manner. There was 0.294 grams thyroid tissue per kgm. of body weight in the dogs with infection, whereas the healthy control animals had only 0.191 grams thyroid tissue per kgm. of body weight.—M. O. L.

Nephrosis of thyroid origin. Davidson, J. R., Canad. M. A. J. 18: 161-164. 1928.

An uncomplicated case of thyroid nephrosis of many years' standing was materially improved by thyroid treatment. A second case, recently developed following influenza, did not respond to thyroid treatment until in addition injections of Collip's parathyroid extract were given, when marked clinical improvement followed, coincident with return of basal metabolic rate to normal. Subsequently the patient was controlled satisfactorily with thyroid alone. In a third case, following a series of unsuccessful pregnancies, in the second month of pregnancy, a definite nephrosis accompanied by a basal metabolic rate of minus 12% was successfully treated with thyroid. It is suggested that cases of nephrosis in which albuminuria precedes oedema by a period of months or years respond more readily to thyroid treatment than when oedema accompanies or immediately follows the albuminuria.—A. T. C.

Preoperative use of compound solution of iodine in exophthalmic goiter. DeCourcy, J. L., Ann. Surg. 86: 871. 1927.

It is now fully established that the pre-operative administration of Lugol's solution to patients with exophthalmic goitre lowers the

basal metabolic rate, controls the toxic symptoms, and lessens the hazards of operation. When the patient has been treated with a preliminary course of compound iodine solution, the thyroid gland at operation is found to be oedematous, so that the gland when sectioned exudes a very watery liquid. This condition is not true of hyperplastic thyroids not treated previously with Lugol's solution nor of ordinary colloid goitre. From this constant observation, the author thinks that the beneficial effects of iodine are brought about by a rapid formation of colloid material in a gland famished for iodine, resulting in back pressure not only on the cells and acini, but also on the thin walled veins surrounding the acini. In the opinion of DeCourcy, this back pressure causes the passive edema.

The swollen condition of the acini renders the secreting cells temporarily inactive, this effectively preventing the absorption of the toxic substance. In course of time however, new blood vessels are formed and the older ones gradually accommodate themselves to the changed condition. The patients once again become toxic with the absorption, even though the colloid formation may still persist in the gland. This explanation would account for the fact that improvement from iodine medication is only temporary.

—Author's Abst.

End-results from the surgical treatment of hyperthyroidism. Frazier, C. H., and W. B. Mosser, J. Am. M. Ass. **90**: 657-659. 1928.

A careful follow-up study on 146 patients who have undergone subtotal thyroidectomy leads the authors to conclude that operative treatment of hyperthyroidism offers a chance for recovery from thyrotoxicosis in about 96% of cases. Complete restitution can be expected in 75% of cases. About 15% will have mild residual symptoms. About 5% will be permanently handicapped. About 3 or 4% will have recurrences. The degree of disability is proportional to the duration of the disease. Early operation will prevent the occurrence of permanent disability.—R. G. H.

Influence of disease of thyroid on menstruation. Gardiner-Hill, H., and J. F. Smith, J. Obst. & Gynec. of Brit. Emp. **34**: 701. 1927; Abst., J. Am. M. Ass. **90**: 806.

An examination made by Gardiner-Hill and Smith of 300 cases of thyroid disease showed that menstruation may or may not be affected in these conditions, but when it is, the alteration tends to be in a uniform direction. The type of menstruation varies inversely with the degree of thyroid activity, i. e., in hypothyroidism there is often a tendency to excessive hemorrhage and in hyperthyroidism, to amenorrhea.

Certain advantages of total thyroidectomy in selected cases of thyrotoxicosis of the exophthalmic type. Gilman, P. K., and W. E. Kay, Am. J. M. Sc. **175**: 350-360. 1928.

From the results of several years observation of thyrotoxic patients by the ordinary surgical means the authors were led to feel that the return to health of many of these patients was incomplete—also that many of them relapsed in spite of good medical care. It appeared that the less of the gland that was left, the better was the ultimate result and the less was the likelihood of a relapse; also the less was the post-operative mortality, the shorter the convalescence and the sooner were the patients able to resume their occupation. It was decided to subject 22 patients to a complete thyroidectomy. Their cases are reported. It was found that the conclusions above mentioned were fully substantiated. Thyroid substance had to be administered, of course, but the regulation of this by basal metabolic determinations was not difficult. Several of the patients were able to determine subjectively the amount of thyroid substance required. Even in the seemingly hopeless cases the results of total thyroidectomy were most gratifying. The patients after long periods of invalidism have resumed their usual occupation and enjoy good health.—R. G. H.

X-ray treatment of goiter. Grier, G. W., Ann. Int. Med. **1**: 241-246. 1927.

This is a clinical paper with no bibliography included. The author believes that radiation can be used successfully in hyperthyroidism if there is no malignancy of the thyroid, or in an inoperable intrathoracic thyroid. He also thinks that hyperthyroidism is a response to toxemia as a large number of his cases had pathological tonsils or infected teeth. Rest, fresh air, good food and sleep are essential to recovery. About six months are required for treatment. With the x-rays one-half an erythema dose is applied to one lobe of the thyroid each week. After two treatments the patient is allowed to rest for two weeks before continuing. When radium is used half an erythema dose of gamma radiation is applied and then repeated in six or eight weeks if necessary. The author prefers the x-rays to radium. A lowering of the pulse rate and a decrease in nervousness is usually noted in a month. Basal metabolism tests should be made and when the rate reaches plus ten or thereabouts the treatments should be discontinued before the thyroid reaches the normal level or the cumulative effect of the radiation may induce hypothyroidism.—E. L.

Studies on the heart in thyroid disease. 1. Changes in the T wave of the human electrocardiogram following iodin medication and thyroidectomy. Hamburger, W. W., M. W. Lev, W. S. Priest, and H. C. Howard, Tr. A. Am. Physicians, **42**: 22. 1927.

Iodin medication (Lugol's solution) in hyperthyroidism results in most instances in diminution of the height of the T wave of the human electrocardiogram. Subtotal thyroidectomy is followed by an even greater decrease in the height of the T, in 3 cases progressing to inversion. Following iodin medication and thyroidectomy the decrease in basal metabolic rate parallels the decrease in height of T. Inversion of T following thyroidectomy occurs as a delayed inversion, in contrast to the immediate inversion from digitalis and the dove-shaped inversion of coronary occlusion.—I. B.

Basal metabolism in organic heart disease. Hamburger, W. W., and M. W. Lev, Tr. A. Am. Physicians, **40**: 159-161. 1925.

Seventy-five per cent of cases of organic heart disease with decompensation show an increased basal metabolic rate of an average of 39% above normal. The rise in metabolic rate is in proportion with the degree of decompensation and the cardiac and respiratory rate. In a case of paroxysmal tachycardia the basal metabolic rate increased 11.1% during the paroxysm. In a normal subject artificially induced tachypnea resulted in a 17.5% basal metabolism increase. The author suggests that probably the increased work of the heart and of the muscles of respiration are the cause of the heightened basal metabolic rate in organic heart disease with decompensation. He also suggests the possibility of the thyroid factor as additionally causative, i. e., the transient hyperthyroidism during decompensation or changes in the thyroid circulation from long-standing congestion.—I. B.

Striopallidal and bulbar symptoms in exophthalmic goiter. Klein, H., Monatschr. f. Psychiat. u. Neurol. **65**: 138. 1927; Abst. Arch. Neurol. & Psychiat. **19**: 358. 1928.

Klein calls attention to the frequent association of exophthalmic goiter with organic diseases of the central nervous system, especially those involving the striopallidal and bulbar regions. He reports a case in which the symptoms referable to the central nervous system ran roughly parallel to the periods of remission and exacerbation of the exophthalmic goiter. Improvement of both symptom groups was marked after each of two operations (partial thyroidectomy). Eventually, certain of the symptoms of exophthalmic goiter disappeared (tachycardia) while others persisted (exophthalmos). The encephalopathic symptoms grew progressively worse. On the basis of this and other cases, as well as because of the relatively frequent finding of intracranial (especially bulbar) hemorrhages at autopsy, he believes that the central nervous lesions are the result of the toxin present in exophthalmic goiter.

The conditions under which iodin will cause a change in the basal metabolic rate in man: I. Its occurrence in conditions other than that of Graves' disease. Martin, K. A., Am. J. M. Sc. **174**: 648-660. 1927.

The effects of large doses of iodin on the basal metabolic rate in patients with leukemia, polycythemia, primary anemia, rheumatic fever, simple goiter and hypothyroidism were studied. It was demonstrated that iodin will lower the basal metabolic rate in certain clinical conditions other than Graves' disease. The increased metabolic rate of patients with leukemia and polycythemia was not affected by ingestion of large doses of iodin. But, the high basal metabolic rate of patients with primary anemia and rheumatic fever was lowered, similar to the results seen in Graves' disease when iodin was given. Furthermore, moderate but constant lowering of the basal metabolic rate, from normal to a subnormal level, was observed when iodin was given to patients with simple goiter showing symptoms of iodin deficiency. Iodin will frequently increase the basal metabolic rate in patients with hypothyroidism or myxedema, providing they have not previously had iodin or thyroid therapy for several weeks. It is concluded, that since iodin is not a specific for Graves' disease in lowering the basal metabolic rate, the mechanism by which the basal metabolic rate is lowered, followed the ingestion of large doses of iodin, is an acute mechanical blocking of the thyroid secretion. The extent to which iodin will affect the basal metabolic rate in any patient, regardless of the diagnosis, depends upon the ability of the patient's thyroid to store iodin.

—Author's Abst.

The effect of hyperthyroidism on the development of intersexual forms in chickens (Influence de l'hyperthyroïdisme sur l'origine des formes intersexuelles chez les Poules). Nevalonnyj, M., Compt. rend. Soc. de Biol. **97**: 1745-1749. 1927.

Dried thyroid was fed over a period of 147 days to 41 chickens varying in age at the start from 18 to 38 days. Four breeds of chickens were used. The plumage showed in each sex modifications to an intersexual type.—J. C. D.

Endemic goiter in Oregon. Olesen, R., Public Health Reports, **42**: 2831. 1927; Abst., J. A. M. A. **90**: 61.

The thyroid survey made by the author in Oregon included 8,171 boys and 9,427 girls attending the senior and junior high schools and the upper grades of the grammar schools in 32 localities. A total of 5,443 enlargements of the thyroid, a percentage of 30.9, was noted among the 17,608 children examined. Thyroid enlargements of all degrees prevailed among the boys to the extent of 22.3%, and among the girls to the extent of 38.3%. The observa-

tion previously made that thyroid enlargements decrease in numbers as boys increase in age, while among girls the involvements continue to increase in number up to the age of 18, was sustained by the survey. Endemic goiter is present to a considerable extent in the seacoast towns of Oregon, mere proximity to the ocean apparently failing to confer the relative freedom from the disease which prevails on Cape Cod, Massachusetts. At the same time there is much less goiter in the seacoast towns in Oregon than in the cities and towns farther inland. The places of birth and the places of previous residence are factors which do not appear to enter into the question of thyroid status among the children of a given community in Oregon. There appears to be no relationship between the amount of goiter in a given community in Oregon and the treatment of the public water supplies by filtration and chlorination. Endemic goiter prevails to a considerable extent in most portions of the state of Oregon. There is much less goiter in Oregon than in Minnesota, approximately the same amount as in Cincinnati, and much more than in Connecticut and Massachusetts. Olesen suggests the probability that iodine prophylaxis has materially altered the usual incidence of goiter in many localities. It may no longer be possible to determine natural goiter rates.

The effect of iodine on creatinuria in hyperthyroidism. Palmer, W. W., Proc. Soc. Exper. Biol. & Med. **25**: 229-230. 1927.

In fifteen cases of true Grave's disease, with a daily creatine excretion of 200 to 1000 mgm., the administration of iodine in the form of Lugol's solution caused a diminution of creatine excretion to less than 100 mgm. In five cases of toxic adenoma relatively small amounts of creatine were observed in the urine, and iodine had almost no effect upon the excretion. The creatinuria of experimental hyperthyroidism was uninfluenced by iodine.—M. O. L.

The thyroid gland in young adults (Über die Bedeutung der Schilddrüsenvergrösserung im jugendlichen Alter fur die Konstitution). Rubens, O., Ztschr. f. Konstit. **13**: 593-601. 1928.

Out of 3000 students, 19-22 years of age, at the University of Freiburg, 728 or 24.3% had enlarged thyroids, mostly of a soft diffuse variety, rarely nodular. Sixty to seventy-five per cent of those with slightly or moderately enlarged thyroid glands were from districts outside of Baden; while 60-70% of those with large and very large glands were from Baden. Body weight and stature of students with an enlarged thyroid were essentially the same as in students with a normal thyroid. The pulse rate while at rest was 6-7 beats per min. higher in students with enlarged thyroids. The pulse rate after exercise and respiratory rate in cases of enlarged thyroids were the same in cases with normal thyroids. Function-

ally it appears that enlarged thyroids are correlated with a slight degree of hyperthyroidism.—A. T. R.

Acid base equilibrium in thyroid disease (El equilibrio acidobasico en las afecciones del tiroides). Saida, M., Arch. Endocrinol. y Nutrición, **6**: 279-283. 1926.

The acid base equilibrium has been very little studied in thyroid disease. The author has investigated this in ten cases and his findings coincide with those published by Walinski and Herzfeld. In nine cases of hypothyroidism of various types the alkaline reserve was studied by Van Slyke's technic. Low values were found. In one case of hypothyroidism a normal titre was found. There appeared to be no clear relation between the degree of acidosis and either the intensity of the clinical status or the level of basal metabolism. It is surmised that the decreased alkaline reserve is due to augmented formation of acid products and diminution of the blood pH in consequence of the augmented oxidation characteristic of hypothyrodism. He has had successful results in the treatment of hypothyroid condition accompanied by acidosis with insulin and large doses of alkali.—E. B.

The effect of thyroxin in disorders related to the glands of internal secretion (Uber die Wirksamkeit des Thyroxin (Schering) bei endokrin bedingten Störungen). Schittenheim, A., and B. Eisler, Klin. Wchnschr. **41**: 935-938. 1927.

The authors made observations to ascertain the comparative effects of thyroxin and thyroid-gland preparations, administered intravenously and by mouth, on both healthy and pathologic human beings. In normal subjects thyroxin increased metabolism. Similar results were obtained in severe cases of myxedema, the patients being restored almost to normal. Intravenous use proved more effective than by mouth, but the latter is preferable in chronic cases. Thyroxin appeared preferable to thyroid-gland preparations since the latter cannot be so readily standardized and are likely to produce undesirable accompanying effects.—E. P. Durrant.

The results of one hundred consecutive cases of hyperthyroidism operated upon. A clinical and histological study attempting to correlate the morphology and clinical picture, with a view to prognosis. Smith, L. W., H. M. Clute, and J. W. Striedler, Surg. Gynec. Obst. **46**: 325-331. 1928.

Relief from hyperthyroid symptoms was complete in 92 cases; the remainder were all much improved. After one year the basal metabolic rate of 19 patients was less than —10% and of these 15 showed clinical symptoms of myxoedema. This result is considered to be due to removal of larger amounts of gland than was done

formerly, and to administration of iodine after operation to prevent hyperplasia. There is little apparent relation between the degree of involution of the gland and the basal metabolic rate or the clinical picture. The pre-operative administration of iodine is one of the chief factors in disturbing this relationship. There is no relationship between the degree of involution and incidence of either lymphoid infiltration or acidophilic cell formation. Acidophilic cells in hyperplastic glands have been found in all the cases which subsequently developed myxoedema.—A. T. C.

The treatment of habitual abortions by thyroid extract (Le traitement de l'avortement habituel par l'extrait thyroïdien). Vignes, H., Progrès méd. **42**: 1255. 1927.

One case report includes the details of three miscarriages occurring at two and one-half, three, and eight months. A weakly positive Hecht reaction led to rather extensive anti-luetic treatment with no improvement in the tendency to abort. Following the third miscarriage, there was sterility for two years. One month after beginning treatment with thyroid extract, pregnancy occurred. A normal full term child was born. The author concludes that slight hypothyroidism is sufficient cause to produce abortion. Also, when slight hypothyroidism is the cause of abortion, the administration of thyroid extract will correct the condition sufficiently to permit normal pregnancy.—J. P. Pratt.

Effect of iodine in toxic adenoma. Youmans, J. B., and R. H. Kampmeier, Arch. Int. Med. **41**: 66-74. 1928.

The response to treatment with iodine in thirty unselected patients with toxic adenoma who were previously untreated with iodine was essentially the same as that seen in unselected cases of exophthalmic goiter. Whatever differences exist are apparently quantitative, not qualitative. No essential difference in the pathogenesis of toxic adenoma and exophthalmic goiter can be assumed to exist on the basis of this response to treatment with iodine.—Authors' Abst.